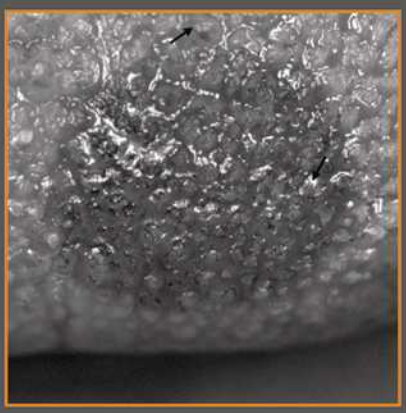

GENETIC VARIATION IN TASTE SENSITIVITY

edited by

John Prescott

Beverly J. Tepper

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Preface

It has been known for more than 70 years that individuals vary dramatically in their sensitivity to the bitterness of compounds containing a thiourea moiety, in particular to phenylthiocarbamide (PTC) and 6-*n*-propylthiouracil (PROP). The investigation of this phenomenon has traveled through various stages. The genetics of PTC tasting were investigated first, showing that up to 30% of individuals were insensitive to its bitterness. Now, we know this may be true only in Western, Caucasian populations. The possibility that inheritance patterns of PTC tasting could differ between cultures and might be a marker for past migration patterns led to a number of interesting cross-cultural comparisons in the literature in the 1940s and 1950s. Later, investigations into the relationship between PTC tasting and food preferences started to explore the wider implications of this trait. Until the mid-1970s, however, sensitivity to PTC and PROP had not attracted significant attention from chemosensory scientists. This situation has changed in the past two decades and measurement of PROP (now more widely used than PTC) has become relatively commonplace. However, as interest in this phenotype began to increase, so did the questions it raised.

Many of these questions concern methodology. It is clear that the original determinations of PROP status, via the measurement of thresholds, do not necessarily reflect the distributions of responses seen when suprathreshold techniques, such as intensity ratings, are used. More re-

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cently, there is evidence that even the type of scale used may be crucial in demonstrating relationships between PROP and other variables, or even in defining the distinct PROP groups themselves. One consequence of these findings has been to generate controversy and even skepticism (reflected in some of these chapters)—If PROP effects are so sensitive to the type of measurement used, can this really be an important phenomenon?

Beyond these methodological debates, however, sensitivity to PROP has been implicated as an important index for a wide range of nutritional behaviors, mediated primarily through variations in sensitivity to food sensory properties. In particular, PROP sensitivity has been linked to perception of fats and bitter antioxidant compounds, such as the phenols found in cruciferous vegetables. In turn, it is assumed that differences in sensitivity mediate preference variations, and hence have explanatory value for nutritional behaviors. The recognition that such behaviors are crucial to major health issues such as obesity, cardiovascular disease, and cancer has therefore added to the impetus to understand individual variations in taste perceptions and preferences.

It is apparent that there is now a sufficient body of work on this phenomenon to warrant reflection on what is known about PROP, to begin identifying gaps in knowledge, and to address future research needs. These issues were the focus of a symposium, "Sensitivity to PROP (6-*n*-propylthiouracil): Measurement, Significance, & Implications," held in July 2002, as a satellite to the European Chemosensory Research Organisation (ECRO) conference in Erlangen, Germany. This volume, based on the presentations at the symposium, captures for the first time the current debate surrounding the significance of sensitivity to PROP and assesses its wider significance.

In addition, interest in this phenotype has clearly extended beyond chemosensory science to other disciplines, including applied sensory science, nutrition, and public health. Workers in these areas have not necessarily been privy to the methodological debates among taste scientists. This volume is a state-of-the-art review of the research being undertaken in this field, and thus a reference for anyone wanting to understand the broader implications of PROP genetics for taste perceptions, food preferences, and health.

These chapters address questions such as:

To what extent is sensitivity to PROP an index of sensitivity to other sensory qualities?

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Does studying PROP sensitivity provide insights into individual variations in food choices and the health consequences of those choices?

Can we account for differences between research groups in findings of associations between PROP and other variables?

While definitive answers to such questions may not yet be apparent, it is hoped that this volume will stimulate further research in this intriguing area and lead to greater cross-fertilization of ideas across disciplinary lines.

We thank all the participants of the symposium whose enthusiasm inspired lively debate. Special thanks are due to the contributors for devoting their time and intellectual energy to writing the chapters that constitute this volume.

Financial support for the symposium was generously provided by International Flavors & Fragrances Inc. and ECRO. Many thanks are due to Dr. Thomas Hummel, who graciously served as the local organizer for this event. Finally, we are particularly grateful to Dr. Carol Christensen at IFF, without whose vision and enthusiastic support this symposium and volume would not have been possible.

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1

Genetic Differences in Human Oral Perception

Advanced Methods Reveal Basic Problems in Intensity Scaling

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I. INTRODUCTION

A. L. Fox, a chemist at DuPont in the United States, discovered taste blindness in 1931. While he was synthesizing phenylthiocarbamide (PTC), some of it flew into the air; a colleague commented on its bitter taste, which Fox had not noticed. Asking others to taste it led to a brief announcement in the Science News Letter (1): 60% tasted it; 40% did not. Fox then collaborated with Blakeslee, a prominent geneticist of the day, to organize an exhibit at the 1931 meeting of the American Association for the Advancement of Science. Attendees tasted PTC crystals and pulled the appropriate lever on a voting machine: 65.5% found the crystals bitter, 28% found them tasteless, and 6.5% perceived other qualities. Subsequent family studies (2,3) suggested that PTC tasting is a dominant genetic trait.

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A. Harris–Kalmus: The Era of Threshold Studies

Identification of perceived quality gave way to the Harris–Kalmus threshold procedure (4). In it, subjects were given eight solutions: four water and four a specific concentration of PTC. Their task was to sort the solutions into two groups. If the subjects sorted correctly, the next trials used successively lower concentrations of PTC; incorrect responses led to higher concentrations. Threshold was defined as the lowest PTC concentration sorted correctly. This procedure is a variant of the classic method of limits devised by Fechner (5), but there is no indication in the Harris–Kalmus paper that the authors knew this. Harris–Kalmus threshold methodology dominated research on taste perception for years, until McBurney replaced it with the more efficient up–down technique (6). In the original form of the up–down procedure, subjects were presented a stimulus and asked whether it had a taste. If "yes," the next stimulus presented was weaker; if "no," the next stimulus was stronger. This generated a series of runs up and down the concentration range near *threshold*. Disgarding the first reversal (a change from "yes" to "no," or vice versa), threshold was defined as the geometric mean of an even number of reversals (typically six). McBurney used the reasoning of Wetherill and Levitt (7) to make this a forced-choice taste threshold. Now subjects must choose the stimulus with a taste between two choices: water and a given stimulus concentration. Since subjects can be correct by chance 50% of the time, the procedure requires two consecutive correct responses before the concentration is lowered, but a single incorrect response causes the concentration for the next trial to be raised. Using this technique, threshold falls about halfway between chance and perfect performance. (See Sec. IV.B.1 for a discussion of some of the limitations of threshold measures.)

Research from this era concluded that the N-C = S group on the PTC molecule [and related compounds such as 6-*n*-propylthiouracil (PROP)] was responsible for its bitter taste. Data from a variety of studies showed that the frequency of nontasters varies by race and hinted that it may vary by sex as well (see Ref. 8 for a confirmation of sex effects using modern statistics). Of special interest, Kalmus showed that the average PTC threshold of tasters with only taster siblings was lower than that of tasters with nontaster siblings (9). This suggested that PTC tasting was an incompletely dominant trait, since the group likely to have the most homozygous tasters had lower thresholds than the group likely to have more heterozygous tasters. A modern analysis of the threshold distribution (10) showed that three distributions can be fit to these data, but the lower two

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(presumably homozygous and heterozygous tasters) overlap extensively. As a result, thresholds cannot be used to classify tasters as homozygous or heterozygous.

An array of studies examined relationships between PTC–PROP status and a variety of genetic and pathological conditions. Among these were two reports with opposite conclusions relating PROP status to cancer of the cervix: One (11) found that tasters had higher cancer rates; the other (12) found that nontasters had higher rates. These studies are of particular interest today because cancer is known to vary with diet, which in turn varies with genetic variation in taste. Could dietary differences across cultures put different PROP groups at risk? Interestingly, Milunicová and associates (11) reported that more cases of breast cancer occurred in tasters. More recently, Drewnoski and colleagues found no association between PROP status and breast cancer (13), but their use of a labeled category scale limited their ability to see any association (see the following discussion and Fig. 4).

B. Fischer: Emphasis on Behavior

In the 1960s, Roland Fischer refined the Harris–Kalmus threshold procedure; he used PROP instead of PTC because PTC has a sulfurous odor and PROP does not. More importantly, he began to examine behavioral and metabolic differences between tasters and nontasters (14). Fischer did all of his research with PROP thresholds; he did not have the advantage of the suprathreshold scaling tools that exist today. Nonetheless, his work showed great creativity and insight. Throughout his career, Fischer distinguished between the bimodal threshold distribution for PROP and the Gaussian distributions for other taste compounds (especially quinine). He argued for a relationship between the two; for example, PROP tasters tended to have lower thresholds for quinine (15,16). Such integration foreshadowed the relationship between PROP and fungiform papillae density that we study today. Fischer was particularly interested in the most extreme individuals, those who had PROP and quinine thresholds that were both very high or both very low. Fischer could not have known that we would discover supertasters on the basis of suprathreshold PROP perception, or that these supertasters would have the highest density of fungiform papillae. Yet his use of both PROP and quinine thresholds to classify subjects may have placed him tantalizingly close to those discoveries, more so than any of his contemporaries.

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Early in his PROP studies, Fischer noted that tasters have more food dislikes than do nontasters (14,17). He described the extremely sensitive tasters of both PROP and quinine as more "slender" than those who were insensitive, and he linked that slenderness to greater number of food dislikes (18). He also observed that the proportion of smokers is lower among those sensitive to quinine (17). At the metabolic level, Fischer made a variety of observations linking PROP sensitivity to hormonal variation. He began with casual remarks about the effects of stress and pregnancy on the variability of PROP thresholds (19), later adding the menstrual cycle as an additional source of variability (20). One of Fischer's most interesting findings concerned two sets of identical twins of whom one twin was pregnant and the other was not; the pregnant twin was more sensitive to PROP in each case. This finding is consistent with other studies associating pregnancy with an increased ability to taste bitterness (21,22), including our own longitudinal study of taste and pregnancy (23). The fact that significant research and discussion continue on these issues reflects Fisher's enduring insight.

C. Suprathreshold Scaling Methods

Early investigators were handicapped by a reliance on thresholds. We have long known that suprathreshold perception of taste is dissociated from thresholds (24–26). In particular, perceived intensity of the bitterness of PROP shows broad variation, even among individuals with identical thresholds (27).

The first suprathreshold study of PTC was published in 1932 by Samuel Fernberger, an eminent psychologist of the day (28). He asked subjects to classify swallowed PTC crystals as "tasteless," "slightly bitter," "bitter," or "extremely bitter," using the taste of "raw quinine" as "extremely bitter" and the taste of "the white of the rind of grapefruit" as "bitter." By assuming that these anchor stimuli taste the same to everyone, Fernberger made a critical error much like the one we discuss in this report. In brief, quinine is not equally bitter to everyone (nor, presumably, is grapefruit rind). By anchoring the bitterness scale to these items, Fernberger could see only relative differences in bitterness for each subject; absolute differences in bitterness across subjects cannot be detected in this manner (29). A similar error in a more recent study (30) was discussed in Ref. 31; we revisit this problem later (see Fig. 3).

The development of direct scaling methods with ratio properties by S. S. Stevens introduced new possibilities to the study of genetic variation

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in taste. However, this methodology is susceptible to misuse because of the fundamental challenge posed by any suprathreshold scaling technique: since we cannot share experiences, we cannot know the absolute intensities perceived by others. Thus, in order to make comparisons across individuals or groups, we must have a standard that can be assumed to be equally intense, on average, to all. Of course, we can never know with certainty whether we have such a standard. Nonetheless, we can make some across-group comparisons if we select a standard unrelated to the domain we are interested in studying (32–35).

In 1975, we used this logic to begin research on genetic variation in taste. We selected NaCl as the standard for our studies because early work suggested that taste blindness was limited to compounds containing the N-C=S group (36). We assumed that even though perceived saltiness probably varies among subjects, that variation would not be systematically associated with PROP status, thereby allowing valid comparisons of average taste intensities between nontasters and tasters.

D. Our Research on 6-*n*-Propylthiouracil: Anatomical Characteristics, Perception, and Behavior

1. Taste Blindness Is Not Limited to the N-C=S Group

The first surprise produced by our scaling studies concerned the association of taste blindness with the N-C=S molecular group. We found that caffeine, which does not contain the N-C=S group, was less bitter to PTC nontasters than to tasters (37). As we became familiar with Fischer's work, we were persuaded to substitute PROP for PTC (38). We presented data showing comparisons of PTC and PROP at the 1982 and 1983 meetings of the Association for Chemoreception Sciences (39,40). Interestingly, correlations between PTC and PROP thresholds were much higher than correlations between thresholds for caffeine and either PTC or PROP (40). The close correlation between PTC and PROP suggests that the two compounds stimulate the same receptor, whereas the looser association between PTC/PROP and caffeine suggests that caffeine binds to a different receptor. We now suspect that the caffeine–PROP relationship and others like it may be produced because the density of fungiform papillae is linked to PROP status (41) (see Sec. I.D.6 for more discussion of this topic).

Another surprise resulted from a study designed to see whether the bitter taste of saccharin is related to PROP status (38); the bitterness is

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more intense to tasters, but so is the sweetness of saccharin, sucrose, and neohesperidine dihycrochalcone [a sweetener derived from grapefruit rind (42)]. Previously taste blindness was thought to relate only to bitterness; these sweetener effects led us to examine other tastants for associations with PROP (31, 43–46).

2. The Discovery of Supertasters

As we continued to study PROP taste, a curious trend began to emerge: Nontasters tended to respond very similarly to PROP, but tasters showed a great deal of variability in the magnitude of perceived bitterness. In particular, one subset of subjects perceived the bitterness of PROP as much more intense than the NaCl standard. We started referring to these subjects informally a "supertasters" and the name stuck (31,45–47).

3. Change from an NaCl to a Tone Standard

During the time we did our early PROP studies, Stevens and Marks were expanding their earlier work on cross-modality matching (48) to create a new method known as *magnitude matching* (49,50). The logic is the same as that described for the NaCl standard used in our early PTC–PROP studies, but the advantage is that we now can select our standard from any modality. One of the most convenient standards used in taste studies is sound (51). By presenting sounds of different intensities and instructing subjects to rate loudness on the same scale used to rate taste intensity, we can express taste intensity relative to sound. For example, assuming equal average auditory capability across groups, supertasters rate the bitterness of 0.0032 M PROP (the highest concentration we use for testing) as considerably more intense than a 1000-Hz tone at 98 dB, medium tasters match this PROP to a sound intensity between 86 and 98 dB, and nontasters match it somewhere between 62 and 74 dB (52).

Magnitude matching with an auditory standard became available just as we were becoming concerned about NaCl as an appropriate standard. The set of taste stimuli with known associations with PROP bitterness was growing. If NaCl taste were associated with PROP status, using it as a standard would diminish the apparent size of PROP effects. We compared NaCl and sound as standards in an early study on sweeteners; the results showed greater effects with the sound standard (42). Continuing efforts using both standards confirmed our initial concerns: NaCl tastes most intense to supertasters and least intense to nontasters (53), meaning that all of the differences we had seen using the NaCl

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standard were underestimates. More recent work has shown that substances with all four of the classic taste qualities (i.e., salty, sweet, sour, and bitter) show positive associations with PROP status when a sound standard is used (54).

In 1994, we introduced the PROP ratio as a convenient scoring system to classify nontasters, medium tasters, and supertasters (8). We developed this measure by testing a series of NaCl and PROP concentrations spanning the dynamic range (i.e., the concentration range over which perceived intensity varies); this allowed us to assess dose–response relationships for each subject. When each subject's NaCl and PROP functions were superimposed, we observed three groups (albeit with some overlap). For most individuals with PROP thresholds above 0.0002M (i.e., nontasters), the PROP function was clearly below the NaCl function. Those with PROP thresholds of 0.0001M or below (i.e., tasters) had PROP functions that matched the NaCl function or markedly exceeded it; supertasters were identified as tasters whose PROP functions most dramatically exceeded the NaCl function. To quantify this, we defined the PROP ratio:

$$\text{PROP ratio} = [(0.032\text{M PROP}/1\text{M NaCl}) + (0.01\text{M PROP}/0.32\text{M NaCl})]/2$$

When we found that NaCl was a poor standard, we constructed a ratio using ratings of sound intensity rather than salt intensity, substituting the loudnesses of 98 and 86 dB for the saltinesses of 1 and 0.32M NaCl, respectively. For supertasters, the ratio based on tones is larger than that based on NaCl, but subjects are similarly rank-ordered by both methods. Thus, the PROP ratio based on NaCl endures as a useful way to classify subjects even though the expression of sensory intensity relative to NaCl makes differences across nontasters, medium tasters, and supertasters appear smaller than they really are.

4. Oral Burn and Oral Touch

We also began to look at foods with tactile [e.g., milk products (55, 56)] and irritant properties (e.g., pepper). Around this time, Karrer was a graduate student in the laboratory working on capsaicin, the active ingredient in chili peppers. She was curious about the ability of capsaicin to desensitize the mouth. While exploring that idea, she discovered an intriguing association between the oral burn of capsaicin and PROP status: tasters perceived the most intense oral burn (57). Later work showed that supertasters derive even greater burn from capsaicin than medium tasters (58).

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5. Anatomical Characteristics of the Tongue

Our understanding of the relationship between oral burn and PROP taste became clear when we began to study anatomical variation on the tongue. We took this new direction under the guidance of Inglis Miller, who worked with the geneticist Glayde Whitney to discover associations in mice between taste bud number and avoidance of the bitter taste of sucrose octaacetate (59). They suggested that "the relative number of taste buds which individual mice and humans possess probably contributes to the relative differences in their taste sensitivity and preference behavior." Miller pioneered the technique of staining the human tongue with blue dye to count fungiform papillae. The dye stains filiform but not fungiform papillae; it also stains taste pores (the conduits to taste buds). Thus, under high magnification, taste pores are visible as small blue dots against the pink background of the fungiform papilla. Miller and his student Reedy showed that in humans, the bitterness of PROP is associated with the number of taste pores (60). In collaboration with Miller, we observed that supertasters have the most fungiform papillae and taste pores (8, 61); since taste buds are surrounded by trigeminal fibers that mediate oral burn (62–65), it makes sense that oral burn is associated with PROP status. (As a historical footnote, this was not Miller's first brush with PROP research: As an undergraduate at Ohio State University, Miller worked as a research assistant for Roland Fischer; this experience strongly influenced his later decision to study with Lloyd Beidler at Florida State University.)

PROP taste is also associated with oral touch, which leads to important differences in the tactile sensations evoked by foods. As with oral burn, this relationship appears to result from anatomical features: Fibers mediating tactile sensation do not cluster around taste buds as do those mediating pain, but fungiform papillae are innervated by fibers mediating tactile sensation (66–68).

6. What Makes a Supertaster?

Nontasters have fewer fungiform papillae than do tasters, so the mechanisms must be related for PROP bitterness and tongue anatomical characteristics. One might then suspect that supertasters are tasters with a high density of fungiform papillae, but the bitterness of PROP shows much greater variation across the three groups than does any other tastant. This has led us to suspect that supertasters may be homozygous for the dominant PROP allele and have a large number of fungiform papillae (41). The greater perceived intensities of oral stimuli other than PROP may be

produced largely by greater numbers of fungiform papillae. Factors that alter taste without altering number of fungiform papillae (e.g., pathological conditions, sex hormones) complicate assessments of the relative contributions of genes mediating these phenotypes (29). Genetic testing may clarify this point.

7. Retronasal Olfaction

One of our newest research directions involves the relationship between oral sensations and retronasal olfaction. Retronasal olfaction results when volatiles in foods and beverages are pumped behind the palate and into the nasal cavity by chewing and swallowing. Although these odor sensations are produced by the activation of olfactory receptors high in the nasal mucosa, their perceived origin is in the mouth. For many years, this localization was thought to be mediated solely by the presence of tactile cues in the mouth, but we have shown that taste input plays a role as well. Unilateral anesthesia of the chorda tympani causes retronasal olfaction to localize to the opposite side of the mouth (69). Most recently, we confirmed this finding by simultaneously anesthetizing the chorda tympani and trigeminal nerves; retronasal olfaction not only localized to the unanesthetized side but also diminished in intensity (70). This finding supports complaints made by patients with oral damage who report that they can smell odors (i.e., orthonasal olfaction) but not experience flavors of foods (i.e., retronasal olfaction). Moreover, it suggests that genetic variation in the perceived intensity of oral stimulation may produce related differences in retronasal olfaction; supertasters may perceive more intense retronasal olfactory sensations than nontasters. We are presently testing this hypothesis (71).

8. Food Intake and Preference

Since PROP affects oral perception, its contribution to food behavior is not surprising. This research is reviewed by Duffy and colleagues in Chapter 1 in this volume.

9. Pathological Conditions and Health Risk

Recently, we have begun to assess PROP effects on the development of various health conditions.

a. Cancer. We have already described early work relating PROP status to the incidence of cervical cancer (11,12), as well as a more recent (but

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flawed) failure to relate PROP to breast cancer (13). Using the more sophisticated scaling techniques described later in this chapter, we have preliminary data linking PROP status and number of colon polyps (a precursor to colon cancer) in a group of older men: The bitterness of PROP was correlated with the number of polyps (72). Consistent with the known risk factors for colon cancer, the men with polyps tended to have higher body mass indexes and to eat fewer vegetables than did those without polyps. This tendency is consistent with the lower vegetable intake and higher body mass indexes associated with males less responsive to PROP.

b. Cardiovascular Disease. The effects of PROP on cardiovascular risk, mediated by food preference and intake, are discussed in detail by Duffy in Chapter 10 in this volume.

c. Oral Phantom Sensations. Mounting evidence indicates that inputs from nerves mediating oral sensation interact in the central nervous system to inhibit each other. Damage to taste thus can have unexpected sensory consequences. Over several years, we have shown that taste loss on the front of the tongue (due to chorda tympani damage or anesthesia) can produce increased taste sensation on the contralateral rear of the tongue, presumably by releasing inhibition on the glossopharyngeal nerve (73–75). Chorda tympani blockade can also lead to increased pain sensation on the contralateral front of the tongue, especially in supertasters, presumably via release of inhibition on the trigeminal nerve (76).

Of special interest, supertasters with chorda tympani blockade can also experience taste and pain sensations in the absence of stimulation. Although there is significant variation in the nature and intensity of these oral phantom sensations, their strength can become a primary health concern. For example, burning mouth syndrome (BMS) is an oral pain condition found primarily in postmenopausal women. Those who experience BMS describe severe oral pain sensations, yet visual examination of the mouth reveals no apparent abnormality. Our research has shown that individuals with BMS tend to be supertasters who show signifcant taste loss on the front of the tongue, especially for bitter stimuli (77,78). This suggests that BMS pain is a phantom sensation caused by release of inhibition: Burning mouth syndrome is especially prevalent in female supertasters because the hormonal changes coincident with menopause result in bitter taste loss. Other common causes of taste loss are head trauma and viral infection (79). Until recently, medical interventions for BMS have largely been ineffective, but work in 1998 by Grushka and her

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colleagues demonstrated that the pain of BMS can be blunted by mild doses of the anticonvulsant medication clonazepam (80). This drug is an agonist of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA); we believe medications like clonazepam may boost inhibitory tone in the higher neural circuits processing oral input. Efforts to characterize these circuits further are ongoing.

II. THE PROBLEM: ADJECTIVE/ADVERB-LABELED SCALES

For almost every PROP effect reported in the literature, there are studies that do not find it. Some have argued that the lack of consensus across PROP studies means that the effects observed are not robust. We strongly disagree. Instead, we propose that this very explanation reveals widespread and fundamental misunderstandings about how scales function. Unless researchers are fully aware of the properties of the scale they use, the results of their work cannot be interpreted in meaningful ways.

Some of the problems that lead to PROP effect failures have been discussed previously; these include scales with ceiling effects that blunt the ability to identify supertasters, inadequate sampling (a serious problem in small studies), a poor choice of standards, and a dependence on thresholds for subject classification. In particular, we have reviewed the impact of these problems on studies involving genetic variation in perceived sweetness (27). However, our recent work suggests that the most egregious problem by far concerns inappropriate use of adjective/adverb-labeled scales. We have identified specific studies affected by this problem (32,34); here we continue with a broader discussion of the problem, its consequences, and some potential solutions.

A. Origin of Adjective/Adverb-Labeled Scales

Grammatically, adjectives modify nouns. Thus, we can use the adjective *strong* to describe the intensity of sensation (e.g., Is that a *strong* taste to you?). Adverbs modify adjectives and can add additional information about intensity (e.g., Is that a *very* strong taste to you?). But for adjectives and adverbs alike, absolute perceived intensity depends on the noun. As S. S. Stevens famously noted, "Mice may be called large or small, and so may elephants, and it is quite understandable when someone says it was a large mouse that ran up the trunk of the small elephant" (81).

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1. Category Scales

Category scales partition domains. For example, various category scales were evaluated by the Natick Army Laboratories (82) to study both hedonic (83) and sensory (84) experiences. In one study, subjects were instructed to rate the intensity of a given taste quality, where 1 = none, 3 = slight, 5 = moderate, 7 = strong, and 9 = extreme. Variants of this scale have been used by many researchers and are sometimes described as *Likert scales* (85). The original scale devised by Likert (86) was a category scale intended to quantify the degree of agreement with statements indicating attitudes.

As Stevens noted (87), the numbers on category scales do not have ratio properties: 8 does not denote an experience twice as intense as 4. Some investigators have used ratios among category ratings to determine PROP status, but these ratios do not have the same meaning as those calculated by using ratings from scales with ratio properties. Nevertheless, since these category scale "ratios" do represent a within-subject comparison, they are probably better than the category ratings themselves for classification purposes (see further discussion later).

2. Visual Analogue Scale

The visual analogue scale (VAS), which has its intellectual origins in the graphic rating scale (88), began to be commonly used in the 1960s (89,90). Typically, it is a line labeled at the ends with the minimum and maximum for whatever sensation is to be measured (91). As an example, Silverstone and Stunkard used a VAS to assess hunger (92); their scale consisted of a horizontal line labeled "not at all hungry" on the left and "as hungry as you have ever felt" on the right. Interestingly, in contrast to the category scale, the VAS appears to have ratio properties (93). Note that the invalid nature of either VAS or category scales for across-group comparisons is independent of their ratio properties or lack thereof.

B. Adjective/Adverb Intensity Labels Do Not Permit Valid Across-Group Comparisons

1. Ratio Scales And Adjective/Adverb Labels

Ratio scales were first used in the 1960s as the result of S. S. Stevens's pioneering work on direct scaling methods (94). The most popular of these

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methods is magnitude estimation. Subjects are instructed to assign numbers to the perceived intensity of their sensations such that the ratios among those numbers are equal to the intensity ratios among the sensations. That is, one taste that is twice as intense as another is assigned a number twice as large.

Borg sought to combine the virtues of the adjective/adverb descriptors and the ratio properties of a magnitude estimate scale (see Ref. 95 for a summary of these efforts). Borg was interested in the ability to compare absolute perceived intensities across individuals and groups. He understood that magnitude estimate data could not be used to make direct comparisons. This fact has not always been appreciated by others (e.g., see Ref. 96 for an invalid comparison of raw magnitude estimates of loudness in young and elderly subjects).

Borg (97) and Teghtsoonian (98) devised range theory. They maintained that sensory range (i.e., the difference between "no sensation" and "maximal sensation") is equal for all individuals and all sensory modalities. If range theory had been correct, a labeled, universal sensory ruler could be constructed by locating the correct positions of adjective and adverb descriptors within the sensory range. Ratings on such a scale would have produced valid comparisons across sensory modalities and individuals and groups. Interestingly, Borg never tried to locate the descriptors empirically, instead placing them at positions that seemed reasonable to him (97).

Range theory is not correct (34). Borg argued in favor of a common maximum across all sensory domains, illustrating this with a pilot study he conducted at a psychophysics conference in 1985. He asked attendees to rate the maxima for a variety of sensory domains (e.g., pain, loudness, brightness, perceived effort/exertion, sweetness) and concluded that they were roughly equal, although he placed pain slightly above the other modalities and sweetness slightly below. Even if this conclusion were to hold with more empirical study (see Ref. 34 for specific proof that it does not), there are many domains with maxima that are obviously weaker. For example, consider sensations such as the odor of roses or the perceived viscosity of fats in foods. For most individuals, these sensations never reach the level of intensity produced by intense sensations in the domains of loudness or pain.

The efforts of other investigators, led by Moskowitz (99), have provided insights about the nature of adjective/adverb descriptors. Moskowitz combined intensity labels with magnitude estimation in a particularly clever way. At the end of a magnitude estimate experiment, he asked

subjects to provide magnitude estimates of the labels as though he had provided stimuli for which those labels were relevant; this revealed the correct spacing of the labels. Moskowitz did this for a variety of food attributes (e.g., sweetness, flavor intensity, consistency, color deepness, and hedonics), and the spacing that resulted was essentially the same for each attribute, similar to the spacing Borg had devised. This was the first demonstration that the relative spacing of adjective/adverb descriptors is largely invariant, but the absolute intensities denoted by the descriptors vary. (Note that this appears to be equally true for sensory and hedonic experience.) A variety of additional studies placing descriptors on ratio scales support roughly the same spacing (57,100–102).

With the Labeled Magnitude Scale (LMS), Green and his colleagues (103) were the first to use both empirically placed descriptors and a maximum on a ratio scale. They correctly suspected that maxima for sensory domains were not all equivalent, so they derived the LMS for oral sensations only. These insights paved the way for the development of the general Labeled Magnitude Scale (gLMS) described later.

In summary, the remarkable agreement among various assessments of the relative spacing between adjective/adverb intensity descriptors on ratio scales underscores our argument that this spacing is virtually invariant. Minor variation among such measurements is to be expected because of the biases associated with psychophysical judgments (104). As we will see, the stable spacing of intensity descriptors on ratio scales permits us to apply appropriate descriptors to any domain of interest with agility.

2. *The Absolute Intensities Denoted by Adjective/Adverb Labels Vary Across Domains and Across Individuals/Groups*

S. S. Stevens's elegant image of the large mouse running up the trunk of the small elephant encapsulates our implicit understanding that intensity descriptors denote different absolute intensities in different domains. Our work on genetic variation in taste illustrates the kinds of systematic variation that can occur across individuals or groups.

a. Variation in Adjective/Adverb Intensity. In the early 1990s, we had just discovered supertasters (47) thanks to our emerging ability to quantify the magnitude of taste differences across tasters. The protocol we used for more efficient classification of PROP status was as follows: Subjects tasted various concentrations of NaCl and PROP and then listened to 1000-Hz tones of varying loudness; stimuli were presented in blocks (i.e., NaCl,

tones, NaCl, tones, PROP, tones, PROP, tones; we now also add another block of tones at the beginning of the session). At the end we followed Moskowitz's suggestion and asked subjects to rate the perceived intensity associated with several adjective/adverb descriptors. During this period, we worried about variation across PROP groups in the absolute intensities denoted by descriptors (105), but we had no idea how large this variation would be.

Normalizing the data (27) to the geometric mean of the tone ratings expressed the perceived intensities of the tastes and descriptors relative to the tones as a standard. These normalized intensities for adjective/adverb descriptors vary with PROP status, as shown in Fig. 1. Of 308 subjects, 9

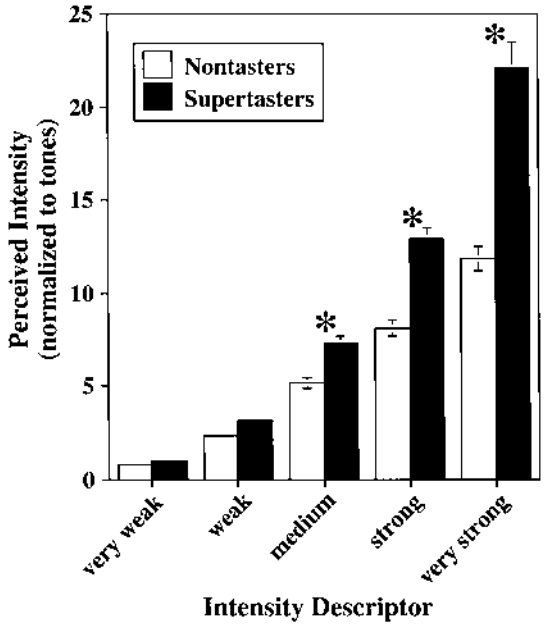

Figure 1 Nontasters and supertasters of PROP differ in the perceived intensity of adjective descriptors. Subjects (75 nontasters, 75 supertasters) rated the perceived intensity of descriptors and PROP by using magnitude matching (magnitude estimation with a 1000-Hz tone standard). Subjects rated PROP first, then tones, then the descriptors. Asterisks denote $p < 0.05$ for planned comparisons following ANOVA. PROP, 6-*n*-thiouracil; ANOVA, analysis of variance.

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showed Mahalanobis distances so far removed from the rest of the subjects ($p < 0.001$) that they were classified as out liers and deleted (106). Of the remaining 299, descriptor ratings from the 25% of subjects with lowest PROP ratings and the 25% with highest PROP ratings are shown. Analysis of variance (ANOVA) revealed a significant main effect of PROP status ($F = 49.212$, $p < 0.0000001$) and a significant interaction ($F = 39.234$, $p < 0.0000001$); follow-up *t*-tests (planned comparisons) showed significant differences for "medium," "strong," and "very strong." Because adjectives were presented at the very end, supertasters experienced very intense tastes followed by tones, whereas nontasters experienced weaker tastes followed by tones. Had the adjectives been presented after the tastes, the differences between ratings for taste adjectives across nontasters, medium tasters, and supertasters would probably have been greater, since the tone loudnesses (much more similar across nontasters and supertasters than were the tastes) could have blunted very different taste experiences.

In addition to the descriptors, normalized intensities for NaCl vary with PROP status; supertasters perceive the most intense saltiness (53). As described earlier, this finding indicated to us that NaCl was a conservative standard (i.e., differences across nontasters, medium tasters, and supertasters measured with an NaCl standard appear smaller than they really are).

b. Remembered Sensations. In her thesis for the Yale University School of Medicine, Fast is using magnitude estimation to quantify the perceived intensity of a variety of remembered everyday sensations. Subjects are presented with lists of common sensory experiences from various domains; taste and oral irritant sensations are presented last to prevent context effects (107). After the remembered sensations are rated, subjects rate the actual sensations produced by NaCl, PROP, and tones. Finally, they are asked to rate the "strongest imaginable sensation of any kind" as well as other descriptors used in the original LMS (i.e., "strongest sensation experienced," "very strong," "strong," "moderate," "weak" and "barely detectable").

Note that this study is modeled on work by Green and coworkers (103) except that sensations are judged in the context of *all sensations of any kind*, rather than *all oral sensations*. Preliminary data ($N = 57$) are shown in Fig. 2. Note that the spacing between adjectives in Fast's experiment is similar to the spacing produced in the Green and associates study; this is the invariant spacing we have already described in which the top of the scale is placed at the sensory maximum. The range of this scale

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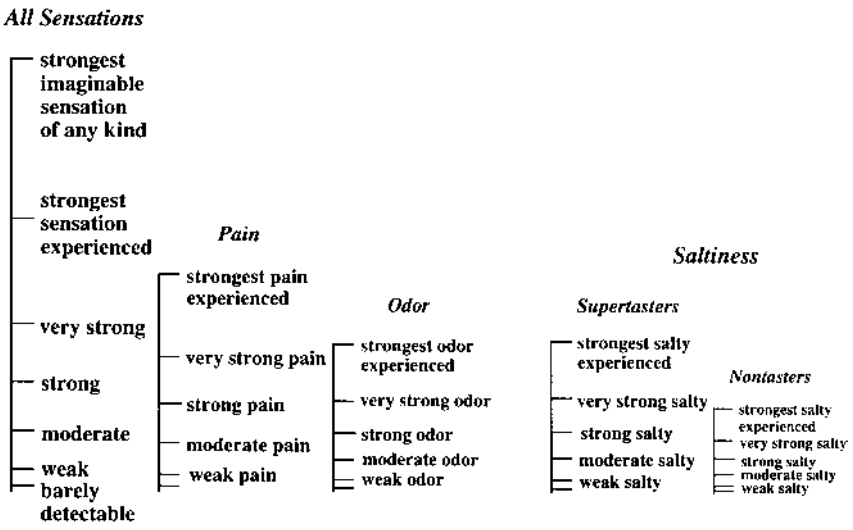

Figure 2 The general labeled magnitude scale (gLMS), left, with suggested labeled magnitude scales for individual domains of remembered everyday sensations including pain, odor, and saltiness, right. Saltiness is shown for supertasters and nontasters. Scales were constructed ($N = 57$) with a procedure modeled on that of Green et al. (103). We suggest that the spacing of the adjectives within each scale is invariant but the top of the scale is determined by the absolute perceived intensity of the domain. For example, the top of the pain scale denotes a greater magnitude than the top of the odor scale.

includes all real or imagined sensations; we call it the *general Labeled Magnitude Scale* (gLMS). To the right of the gLMS in Fig. 2 are examples of LMSs constructed for individual domains. The location of the top of each scale relative to the gLMS was determined empirically as the average location across subjects. These scales illustrate our argument that the relative spacing of adjectives is invariant, but the intensity range of scales is determined by the absolute perceived intensity of the label at the top.

Our decision to use the label "strongest imaginable sensation of any kind" as the top of the intensity scale was initially based on concerns that the top anchor on the original LMS ("strongest imaginable oral sensation") might denote a stronger absolute sensation for supertasters. Out of caution, we used "strongest imaginable sensation of any kind" (27), although at the time it would have been reasonable to assume that oral

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pains not related to PROP status (e.g., toothache) would represent the most intense oral sensation to everyone. To test this, we collected questionnaire data in which subjects rated the strongest oral burn (e.g., chili pepper) and strongest oral pain (e.g., toothache) they had experienced. These data showed that oral burn is more intense than oral pain to supertasters (34, 108), indicating that the original LMS underestimates the size of differences across nontasters, medium tasters, and supertasters.

Does the use of remembered sensations compromise the stability of scales? More specifically, how do subjects interpret the word *imaginable* when using the gLMS? Although most subjects seem to draw realistic inferences about their sensory abilities under maximal stimulation, not everyone is so reasonable. In one spectacular example, a subject described "strongest imaginable sensation of any kind" as appropriate to the sensations evoked by "being sucked into a black hole." Because of the potential for confabulations of this sort, we instruct subjects that "imaginable" sensations should apply to situations that could reasonably occur. In general, the utility of using the word *imaginable* remains to be evaluated.

3. Inappropriate Label Use Produces Invalid Comparisons

Once it becomes clear that the spacing of adjective/adverb labels does not vary but that the absolute intensities denoted by those labels do, it is important to show how the VAS and category scales produce invalid comparisons across individuals and groups.

a. Errors in PROP Studies. We still do not know exactly how subjects attach intensity labels to their experiences. For example, we assume that "very strong taste" denotes the appropriate location of "very strong" in the domain of taste experiences for an individual subject. But, in one study, we found that a substantial number of supertasters rated the actual taste of PROP as more intense than their earlier rating for "strongest bitter taste ever experienced" (34). What does this mean? Do the intensities of taste memories fade with time? Had these subjects never before encountered a bitter stimulus as intense as PROP? We suspect the latter explanation and caution that the stimuli given to subjects may reset the absolute intensities denoted by descriptive labels.

Using PROP taste, Fig. 3 illustrates the errors generated in scaling studies when one assumes that intensity adjectives denote the same absolute intensity to everyone. Note that the degree to which comparisons are invalid depends on the relative size of group differences in adjective/

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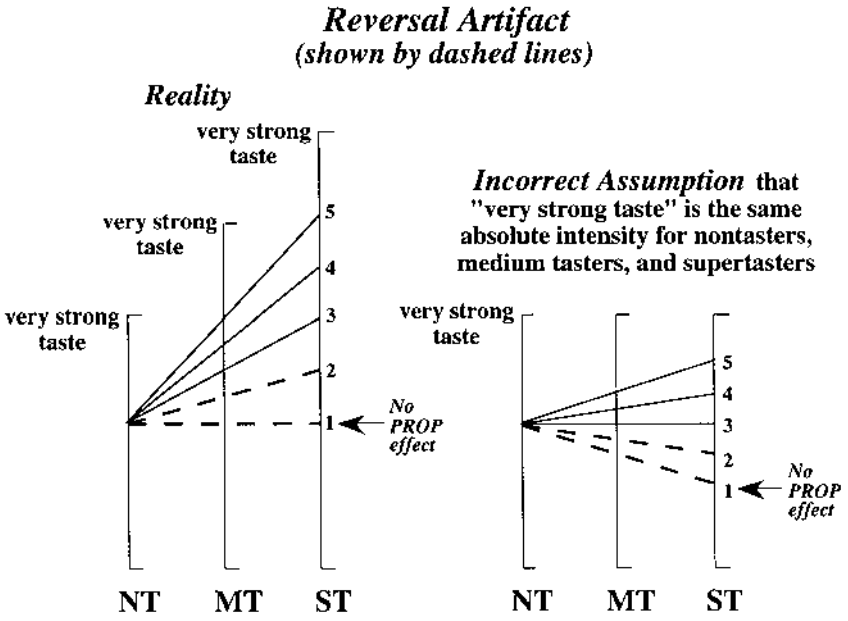

Figure 3 True differences are reduced, hidden, or reversed when one incorrectly assumes that scale descriptors denote the same intensity to everyone. The left side illustrates true differences in taste across nontasters (NTs), medium tasters (MTs), and supertasters (STs). The right side shows how those differences appear under the incorrect assumption that "very strong taste" denotes the same absolute intensity to all. PROP, 6-*n*-propylthiouracil. (From Ref. 33.)

adverb usage, compared with absolute differences for the attribute being measured. Reality is shown on the left; on the right, we see a world distorted by the incorrect assumption that the label at the top of the scale denotes the same absolute perceived intensity to all. The PROP effect labeled 5 denotes a taste perception difference across nontasters, medium tasters, and supertasters that is larger than the group difference in intensity experiences described by the label at the top of the scale ("very strong"). As a result, the difference for 5 shown at left will appear even when "very strong" is erroneously thought to denote the same experience for all subjects (as seen at right). On the other hand, the PROP effect labeled 3 shows the same group difference in sensation as the intensity experience denoted by the label. In this case, the PROP effect disappears when the top

of the scale is treated as equal to all. Finally, when the PROP effect is smaller than the group difference in label use, we see a reversal: a PROP effect that is small in reality now appears to go in the wrong direction.

This argument explains how studies using the VAS or category scales can find small PROP effects or no effects at all, even when these effects are robust. We tested this idea directly by assessing the sweetness of sucrose among panelists in an industrial setting using both the 9-point category scale used by Drewnowski (109) and our gLMS. (At the time, we still called the scale the LMS, but our instructions to subjects indicated that they were to consider "strongest imaginable" in the context of all sensations.) The gLMS produced a significant correlation between PROP bitterness and sucrose sweetness, but the 9-point scale failed to do so (110).

This argument also explains reversals, cases in which tasters or supertasters give ratings that appear to be lower than those given by nontasters but in fact are not. We observed an example of this several years ago (31) in a study that did not find PROP effects in the perceived bitterness of quinine and KCl (30). More recently, a study measuring sensory ratings of creaminess noted that supertasters give slightly lower ratings than other groups for mixtures of milk (3.5% fat) and sucrose (see Fig. 5 in Ref. 111); studies with the gLMS show that sweetness (27) and the creaminess of milk fat (112) are more intense to supertasters.

Further examples of the problems associated with scale misuse are found in Fig. 4, which shows published cases of PROP data collected with category scales (113,114). Note that the gLMS shows that functions for nontasters, medium tasters, and supertasters diverge as concentration increases. We argue that this is the most accurate picture of the reality of these experiences that currently exists. The divergence of these functions is the reason we recommend the use of high concentrations of PROP for subject classification. The PROP functions obtained with category scales cannot show this divergence. Again, the problem is twofold. First, category scales have ceiling effects, especially for supertasters (27). When medium tasters and supertasters are not correctly identified, any effects that depend on this distinction are lost. Second, the top of a category scale denotes a different absolute perceived intensity to nontasters, medium tasters, and supertasters. This means that even if category scales did not have a ceiling effect, they would still fail to distinguish correctly between medium tasters and supertasters.

Figure 1 also shows a problem with the identification of nontasters. Note that the responses to the highest PROP concentration from nontasters are very low when the gLMS is used and much higher when the

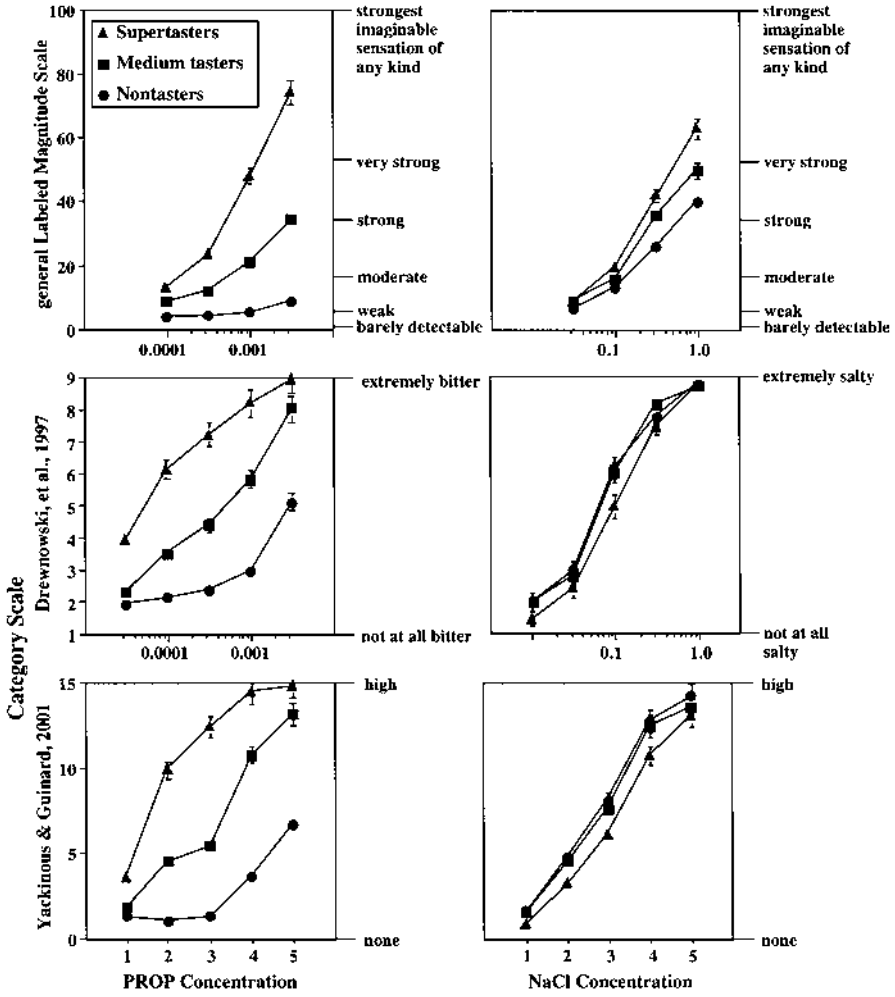

Figure 4 In the category scales, the erroneous assumption that adjective/adverb descriptors applied to oral sensations denote the same absolute intensities to all produced erroneous comparisons across nontasters, medium tasters, and supertasters. Psychophysical functions of PROP (left) and NaCl (right) are shown using the gLMS (top) and both 9-point [(113); middle] and 15-point [(114); bottom] category scales. The gLMS produced functions that diverge for taster groups, whereas the category scales failed to show that divergence. Note that NaCl ratings with the category scales show the reversal effect illustrated in Fig. 3. PROP, 6-*n*-propylthiouracil; gLMS, generalized labeled magnitude scale.

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category scales are used. This could reflect poor selection of cutoffs for the identification of nontasters, but it could also relate to the scale problems under discussion here. The adjective labeling the category scales denote weaker absolute intensities to nontasters, so nontaster ratings appear erroneously high when compared with ratings from medium tasters and supertasters.

In sum, the three taster groups cannot be unambiguously separated with category ratings like those shown in Fig. 1. Since separating groups by responses to the top concentrations tested would certainly fail, both Drewnowski and associates (113) and Yackinous and Guinard (114) used lower concentrations as well as higher ones to separate subjects; they also used ratios of PROP to NaCl. Although the ratios of category ratings are not an accurate representation of real-world ratios of intensity experiences, these "category ratios" produced rough within-subject comparisons. In general, individuals for whom PROP is much more intense than NaCl would produce larger ratios than individuals for whom the two were equivalent; these in turn would be larger than those of individuals for whom PROP is much less intense than NaCl. Unfortunately this does not solve the problem created when very low concentrations of PROP and NaCl are used to construct ratios, since the groups overlap substantially for the low concentrations.

The NaCl ratings in Fig. 4 also reveal a reversal effect. Note that the category scales produced lower NaCl ratings for supertasters than for nontasters and medium tasters. This same reversal for NaCl is shown elsewhere by Drewnowski and associates (see fig. 3 in Ref. 115).

b. Beyond Taste: Errors in Pain Studies. The problem we have described for taste studies is a problem for other research areas as well. One area that has obvious health implications is pain assessment. Category scales and the VAS are commonly used to assess pain in the laboratory (e.g., see Ref. 116 for a VAS anchored with "no pain at all" at one end and "the most pain imaginable" at the other) and the clinic (e.g., see http://www.ynhh.org/choice.pain_ed.html for a 10-point scale with "no pain at all" at 0 to "the worst pain you've ever experienced" at 10). These scales are adequate for measuring within-subject changes in pain, but they are invalid for making across-group comparisons whenever there may be systematic variation in the absolute magnitude of the label "worst pain you have experienced." This would include comparisons by sex, age, race/ethnicity, clinical condition (e.g., childbirth vs. broken limb, cancer vs. healthy), etc.

c. What Can We Do with the Many Studies Making Invalid Across-Group Comparisons? In some cases there is no remedy available. For example, in

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PROP studies the original determination of group membership is itself often flawed. But in cases in which group membership is not in doubt (e.g., sex, age, clinical status), we can assess the potential for group differences in the absolute intensities denoted by scale labels. For example, in the pain study noted previously (116) the authors used their VAS to assess pain differences between women and men. Different experiences might make that label denote different absolute levels of pain in the two groups. We could recruit equivalent groups, asking subjects to rate the "the most pain imaginable" on a valid scale (e.g., magnitude matching or the gLMS). If the group ratings were the same, we could accept the conclusions in the study. If the group ratings were different, the study might be corrected by using the information provided by the different ratings or it might be redone.

d. Valid Uses of Conventional Visual Analogue and Category Scales. In their present, commonly used forms, the VAS and category scales are *valid* for within-subject comparisons; they are also *valid* for across-group comparisons *if and only if* group members have been randomly assigned. These scales are *invalid* for across-group comparisons whenever there is systematic variation in the absolute perceived intensities denoted by the scale labels.

e. Scales in Which No Domain Is Specified. Both the VAS and category scales can be used without specifying a domain (e.g., a VAS could be labeled "zero" at one end and "very strong" at the other). Some studies have used scales with no labels at all (e.g., the tape-pull method). But avoiding labels does not prevent invalid comparisons; in fact, it raises uncertainty about the subject's interpretation of the task at hand. Our anecdotal experience, along with published reports like those shown in Fig. 4, suggest that subjects define an unlabeled category scale in the context of the stimuli they expect to encounter. This possibility warrants further study.

C. Other Researchers Have Observed This Problem

Aitken (117), who made the VAS prominent was aware that it should not be used to make across-group comparisons. He noted, "The same word used by different people need not convey that they experience the same feeling, neither does comparable positioning of marks on lines." But by 1975 there was already an example of inappropriate use. In it, the effects of fenfluramine on hunger ratings were compared for males and females (118). If there were any systematic differences between male and female subjects with regard to hunger experiences, then descriptive adjectives for

hunger would denote different absolute intensities to the two groups. Aitken knew that adjective labels on the VAS must denote equal average intensities to different groups if across-group comparisons were to be made, but this requirement was lost over time as the VAS gained, widespread use.

There have also been previous warnings about the consequences of invalid comparisons. Narens and Luce (119) noted the inaccurate belief held by some economists that perceived value could be compared across individuals. They provided a delightful example that highlights our woeful ignorance of value judgments made by others: We may introduce two people and predict that they will be compatible, only to find ourselves quite mistaken. Biernat and Manis (120) noted that "very tall" indicates a different height when applied to a woman than when applied to a man. Birnbaum (121) showed that a study can be made to produce absurd results when comparisons are made across groups using different contexts to make judgments. He asked different groups to judge the size of the numbers 9 and 221 on a 10-point scale ranging from "very very small" to "very very large." The number 9 by itself suggests a context of small numbers, leading subjects to judge it fairly high; the number 221 suggests a context of much larger numbers, so subjects rate it lower. Accordingly, the average scale values for 9 and 221 were 5.13 and 3.10, respectively, leading to the absurd conclusion that 9 is greater than 221.

Incidentally, frequency and probability terms can also denote very different magnitudes across subjects and groups (122–127). This fact is used to humorous effect in a wonderful scene from the Woody Allen film *Annie Hall*. Alvy (Allen) and his partner Annie (Diane Keaton) appear in split-screen sessions with their respective psychiatrists, who ask about the frequency with which they have sex. Alvy answers, "Hardly ever"; Annie answers, "Constantly." Then both add, "Three times a week."

III. BUILDING A BETTER SCALE: ADJECTIVE/ADVERB-LABELED SCALES CAN PRODUCE VALID ACROSS-GROUP COMPARISONS

A. Magnitude Matching

The gold standard method for making valid across-subject comparisons, magnitude matching, depends on the selection of a standard that is

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independent of the domain to be measured. As discussed previously, we began our PTC/PROP studies using NaCl as our standard and later switched to sound. We ultimately found that NaCl as a standard makes differences across nontasters, medium tasters, and supertasters appear smaller than they really are; sound is better, but it may also have limitations (see the discussion of Fig. 5). Overall, magnitude matching remains the best method we have for making valid across-group comparisons, but the choice of standard is critical.

B. General Labeled Magnitude Scale

We initially created the gLMS simply by changing the top label of the LMS. Since then, we have produced the scale in the same empirical way that Green and colleagues (103) produced the LMS (see the leftmost scale in Fig. 3). These two scales are essentially the same. In fact, we argue that in any domain of remembered or real sensations one studies, the spacing of the descriptors will be essentially invariant and only the absolute intensities denoted by the descriptors will vary.

1. Is the Generally Labeled Magnitude Scale a Universal Sensory Ruler?

Whether or not the gLMS will behave as a universal sensory ruler remains an open question. We know that sensory and hedonic maxima vary across domains. We also know that the maximum within a domain varies across individuals. So, to the extent that the maximum of all domains is sufficiently stable across subjects, the gLMS would be a universal sensory ruler. This is almost certainly not the case, but even if there remain differences across individuals, we can reasonably assume that the maximum of all domains is unrelated to the small subset of domains we are interested in studying (e.g., taste). Note, however, that for taste and any other domain, this assumption requires empirical validation.

To test the validity of across-group comparisons of PROP taste using the gLMS, we asked 100 subjects to rate the bitterness of PROP by using both magnitude matching with a tone standard and the gLMS; scale order was counterbalanced. As shown in the top panel of Fig. 4, we found that the differences among nontasters, medium tasters, and supertasters were about the same size with either method (128). These converging operations

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based on very different assumptions strengthen the conclusion that both are valid scaling procedures for PROP studies.

2. Remembered Sensations as Standards

Magnitude matching was devised by using standards that were actually presented to subjects. However, we can also ask subjects to rate the perceived intensities of remembered sensations (108). This permits us to use remembered sensations as standards, since the labels on the VAS and category scales can be applied to sensations occurring in both reality and memory.

This proved useful in a study comparing the sensations produced by NaCl in young and aged females (129). Concentrated NaCl was rated as more intense by older subjects; this result occurred both with raw gLMS ratings and with gLMS ratings normalized to remembered nonoral sensations. Since NaCl produces both taste (salty) and trigeminal sensations (sting), this finding could reflect an intensification of trigeminal sensations as a result of taste loss. This study provides an example of the power of using remembered sensations as standards within a gLMS study. Normalizing gLMS ratings to standards is magnitude matching. The conclusions of the study were thus checked with methods using two different sets of assumptions: the gLMS and magnitude matching.

Interestingly, the brightest light ever seen (usually the sun) has turned out to be an especially useful standard. Perhaps one of the reasons for its utility is that it is experienced universally by sighted subjects.

3. Using the Visual Analogue Scale for Valid Across-Group Comparisons

The logic introduced thus far allows us to construct a VAS that permits across-group comparisons: We can label a line "zero" on one end and "strongest imaginable sensation of any kind" on the other end. Note that the resulting VAS is identical to the gLMS with its inside labels removed. The key distinction is that the scale labels now refer to experiences not strictly related to the domain of interest.

C. Can We Create a Scale That Produces Valid Comparisons Across Ungrouped Individuals?

We are now exploring the possibility that the logic described might be extended to produce scales providing valid comparisons across individuals

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(see Ref. 130 for preliminary results). In Fast's study (described earlier), after rating the remembered sensations, subjects were presented with various concentrations of NaCl and PROP as well as tones of varying loudness. When each subject's ratings were expressed relative to the rating for "brightest light ever seen" (usually the sun), most nonoral sensations did not correlate with PROP bitterness, but taste and oral burn did. Figure 5 shows relative locations, on average, of some of the nonoral sensations.

Our goal now is to identify an array of everyday sensations that covers a large sensory range and is relatively stable across subjects; that array can then act as a ruler. Sensations likely to show significant variation across subjects (e.g., taste, pain) could then be quantified by locating their intensities in the array. For example, the strongest tastes reported by nontasters and supertasters are shown in Fig. 5. Note that supertasters rate their strongest taste sensation between the strongest odor and the brightest light; nontasters rate their strongest taste near the heat felt when touching an oven door.

Interestingly, this study also found that "the loudest sound ever heard" correlates with PROP bitterness. This has led to concern that hearing may not be sufficiently independent of taste to serve as a good

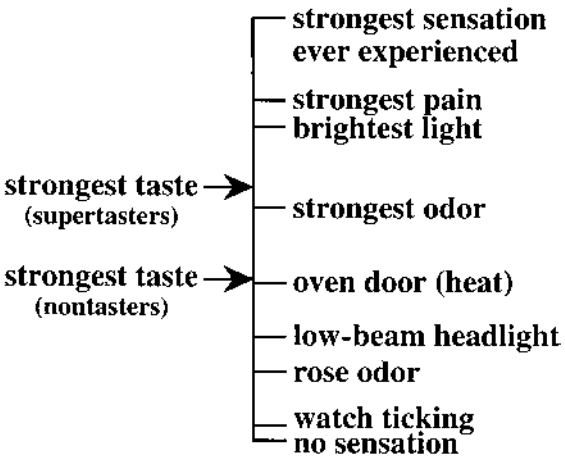

Figure 5 Relative locations of remembered nonoral sensations produced in 57 subjects who were also classified as PROP nontasters and supertasters by using the gLMS. The remembered sensations were normalized to the "brightest light ever seen." The remembered strongest taste was reported as more intense to supertasters than to nontasters; the remembered sensations on the right did not show PROP effects. PROP, 6-*n*-thiouracil; gLMS, generalized labeled magnitude scale.

standard in magnitude matching studies on taste. Since the chorda tympani taste nerve travels through the middle ear on its way to the brain, a variety of ear diseases may influence taste perception. As we explore further sensory standards for use in magnitude matching, we may find that PROP-related differences are even larger than those indicated by our studies using a sound standard.

IV. PROP TESTING: AN OVERVIEW OF BEST METHODS

Techniques for suprathreshold psychophysical comparisons are fundamentally compromised by the fact that we cannot share the experiences of another. The methodology we have described thus far represents the best attempts by our group and others to allow valid across-subject comparisons to be made. These are not perfect methods, but we believe that they have produced increasingly accurate reflections of real-world experience. As a result of this, the widespread influence of PROP taste perception on broader oral sensation, food choice, and disease risk has become more evident. For this reason, it is more important than ever that relationships with PROP be measured appropriately. Over the years, a number of best practices have developed for experiments in which PROP taste will be assessed. Although not exhaustive, the following discussion summarizes factors that should be considered in the design of these studies.

A. Context Effects

The variation in perceived PROP bitterness induces variable context effects in the stimuli that follow. Thus, PROP should be tasted last or on a separate occasion. Other oral stimuli (e.g., capsaicin) can produce context effects as well, so similar care must be taken. In general, the potential for context effects must be considered when interpreting taste studies.

B. PROP Classification

1. Thresholds

Thresholds cannot identify supertasters because threshold and suprathreshold measures are often discordant. For individuals who are nontasters by threshold, perceived bitterness may grow rapidly above threshold; also, for individuals who are tasters by threshold, perceived bitterness may grow

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very slowly above threshold. This confounds taste assessments made with only low concentrations. Pathological conditions may play a role in this dissociation; until genetic testing is possible, we cannot solve this puzzle. At higher concentrations, functions for the perceived bitterness of PROP diverge for nontasters, medium tasters, and supertasters. Thus supertasters are best identified by using suprathreshold measures of responses to high concentrations of PROP (e.g., 0.0032 M, 0.001 M).

When thresholds are of interest, the classic Harris–Kalmus method has been replaced by the more efficient up–down method (see earlier discussion). The up–down method was derived from Fechner's classic method of limits. With the up-down method, it is important to determine the threshold by using an even number of reversals in order to balance biases associated with the presentation of ascending and descending concentrations (131). The threshold is defined as the geometric rather than the arithmetic mean of the reversal concentrations, since concentrations in taste are presented on a log scale.

In addition to conceptual limitations, other sensory components (e.g., odors, trigeminal sensations) of taste stimuli provide a practical barrier to the determination of genuine taste thresholds. For example, the odor of PTC and trigeminal sensations associated with it can produce erroneously low thresholds in nontasters. Trigeminal sensations are generally a problem in taste studies; we have seen clinical cases in which taste was totally absent but "taste" thresholds for many stimuli were close to normal beause of the patient's ability to discriminate water from a dilute concentration by nontaste cues.

2. PROP Tasting and Anatomical Characteristics

PROP tasting and fungiform papillae density are related but not identical measures of PROP status. They may be related by genetic linkage, but that relationship is probably influenced by pathological conditions. Fungiform papillae remain present in humans even when the chorda tympani nerve is severed (132), so taste perception can change via pathological states or hormonal fluctuation while fungiform papillae density remains unchanged. These two measures associate differently with different food attributes.

3. Suprathreshold Scaling

Cutoffs to separate medium tasters and supertasters are somewhat arbitrary. When a study is focused on differences between genetic groups, one can use very conservative criteria (e.g., top and bottom 10% of normalized

PROP ratings to identify supertasters and nontasters). When a study focuses on associations between sensation and food behavior, group classification may cost sensitivity. If PROP bitterness is treated as a continuous variable, one can compare PROP intensity distributions across relevant groups (e.g., sex) by using the chi square statistic; this may be a more sensitive approach.

4. Pathological Conditions

Pathological conditions affect PROP classification by either threshold or suprathreshold means. For example, when tests reveal taster children with nontaster parents, the experimenter should consider the possibility that one or both parents have sustained taste damage. A spatial taste test is one way to find evidence of damage to one or more taste nerves.

C. PROP Status and Food Behavior

The causes of associations between PROP status and food behavior may be complex. Genetic taste status does not change across the lifespan, but the ability to perceive oral sensations does. Does food behavior reflect one's original gentic endowment, taste stimulation experienced at critical development periods, current taste experiences, or a combination of factors? Research in this area continues.

D. Suprathreshold Scaling

1. Using a Standard

The choice of standard (e.g., actual stimulus, remembered sensation) is crucial for looking at sensory/hedonic sensations associated with PROP status. The standard must be unrelated to taste and should be presented in the same session as the stimuli to be evaluated. Data collected using a standard must be normalized. For example, suppose we were to normalize data to the rating for "brightness of the sun" (brightness). First, we would calculate the median rating for brightness for the entire sample, after which we would calculate a normalization factor (NF) for each subject:

$$NF = \text{median rating for brightness/subject rating for brightness}$$

Each subject's ratings for all stimuli would be multiplied by the NF for that subject. In the resulting data set, each subject's normalized rating for

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brightness is equal to the median for the group. This procedure ensures that normalized ratings remain close to the original ratings for most subjects.

The concentration range most commonly used for PROP assessments spans from 0.000032 M to 0.0032 M in half-log steps (i.e., 0.000032, 0.0001, 0.00032, 0.001, and 0.0032 M). Concentrations are spaced in log terms because equal concentration increments on a log scale produce roughly equal increments in perceived intensity. The NaCl concentration series approaching the same intensity range for medium tasters is 0.01, 0.032, 0.1, 0.32, and 1M; tone intensities within this range for medium tasters are 50, 62, 74, 86 and 98 dB.

2. Adjective/Adverb-Labeled Scales

As this chapter has noted repeatedly, adjective/adverb labels must denote the same average perceived intensities to each of the groups being compared. The context of the label should be specified, and that context must be unrelated to the difference under study.

3. The Visual Analogue Scale and Across-Group Comparisons

By definition the VAS has a range from "zero" to the "most intense" of whatever sensory/hedonic experience is measured. To permit valid comparisons across groups, the top of the scale must be related to an experience unrelated to the experience being assessed. A simple solution is to express the top of the VAS as the strongest of all sensations (e.g., "strongest imaginable sensation of any kind") rather than just the strongest sensation in a given domain of interest.

4. Future Directions in Scaling

Note that our current understanding of the logic of across-subject across-group comparisons allows us to determine which scaling methods *cannot* provide valid comparisons. We know much less about methods that *can* provide valid comparisons. To date, magnitude matching (with a standard unrelated to taste) and the gLMS are scaling methods for which some validity has been established. Further research is warranted.

V. SUMMARY AND CONCLUSIONS

The psychophysical study of genetic variation in taste began with thresholds. Once the limitations of thresholds were appreciated, we became

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interested in studying this genetic variation with the suprathreshold scaling methodologies developed by S. S. Stevens. But this posed a problem: Those methodologies permitted only within-subject comparisons of perceived intensity; across-subject or across-group comparisons were invalid. However, the discovery that we are able to match perceived intensities across many different sensory domains provided a solution to this dilemma: We can select one domain as a standard and express sensations from the domain of interest relative to that standard. This is the essence of magnitude matching. The key requirement for across-group comparisons is that sensations from the standard and the domain of interest be independent. We first used NaCl as our standard, but it turned out not to be independent of PROP. We then used sound as our standard and found, as predicted, that differences across PROP groups were larger than they had appeared with the NaCl standard. We plan to continue our exploration of standards. If sound is not independent of PROP, then PROP effects may be even larger than they appear in our current work.

Other studies have relied primarily on adjective/adverb-labeled category or visual analogue scales. Failures to replicate the results obtained with magnitude matching have led us to examine the properties of adjective/adverb-labeled scales. We found, as had others before us, that the absolute perceived intensities denoted by these labels are not constant across domains or subjects. Rather, these scales are elastic. They stretch or compress to fit various domains, and they stretch or compress to fit the range of experiences encountered by individuals. Whenever such scales are used to compare perceived intensities across groups with systematically different experiences, the resulting comparisons are invalid. Specifically, nontasters, medium tasters, and supertasters live in different taste worlds, so the absolute perceived intensities denoted by adjective/adverb descriptors are different for these groups. As a result, comparisons across nontasters, medium tasters, and supertasters using conventional category and visual analogue scales are invalid. With the gLMS, we have explored one attempt to produce an adjective/adverb-labeled scale that can produce valid comparisons. By "stretching" the intensity rang of the scale to its maximum by anchoring it at the top to "strongest imaginable sensation of any kind," we have been able to produce the same separation of taster groups produced by magnitude matching.

Although some existing studies of PROP are rendered invalid by these discoveries, the positive effects of recognizing and correcting these errors offer exciting new research directions ripe for study. Appropriate quantification of genetic variation in taste reveals associations between

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oral sensation and food preferences that in turn contribute to the health risks associated with dietary choices. The new methodology produced here has widespread applications for sensory and hedonic assessment, especially in situations in which we need to compare groups that vary systematically in their sensory experience.

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2

Progress in Human Bitter Phenylthiocarbamide Genetics

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I. INTRODUCTION

Phenylthiocarbamide (PTC) is a chemical compound that tastes bitter to some people but not to others. Individual differences in recognition threshold are partially determined by alleles at a putative bitter receptor gene on chromosome 7 (TAS2R38), but it is not known to what extent these alleles determine sensitivity to bitter compounds within the same chemical class or to other taste qualities. Since propylthiouracil (PROP) has replaced PTC as a taste stimulus in recent studies, it is important to test the relationship between alleles of this gene and PROP sensitivity. Because the density of fungiform papillae on the tongue predicts perceived taste intensity, this trait may partially account for higher than average perceived intensity for these bitter compounds of some individuals and may interact with genotypes at the putative bitter receptor TAS2R38. Although alleles of the gene on chromosome 7 are related to PTC sensitivity, several lines of evidence suggest that other major genes influence the PTC trait as well as sensitivity to PROP and other compounds in this chemical family. Therefore, identification of genetic loci that modify this trait will contribute to our understanding of individual differences. Since bitter insensitivity is a common trait that is perhaps related to food intake and thyroid metabolism, it may have serious consequences for human health.

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II. THE BIOLOGICAL IMPORTANCE OF THE PTC SENSORY POLYMORPHISM

People differ in their sensitivity to taste stimuli, but usually these differences are small (1–3). For some compounds, however, there are large differences in sensitivity. The best-known example of these extreme differences is bitterness of PTC and PROP, chemicals with related structures. Approximately 30% of the Caucasian population is insensitive to the taste of PTC and PROP (4–6). Although other gustatory deficits have been discovered (7–9), PTC sensitivity is the classic example of extreme individual differences in gustatory experience and has been studied since the 1930s.

The proportion of subjects who are insensitive to PTC at low concentrations has been measured in many populations around the world (10). In all human populations tested, from the indigenous people of North America to the indigenous people of Australia, some proportion of people are insensitive to PTC. There have been reports of associations (or lack of associations) between PTC taste status and diseases and traits not directly related to taste. These include diabetes (11–17), dental caries (18), eye disease (19–22), thyroid disorders (15,23–39), schizophrenia (40,41), gastrointestinal ulcers (42–44), depression (45,46), personality characteristics (47–49), mental function (50–52), growth variation (53,54), tumors (55,56), and susceptibility to infectious disease (14,15,57–61). The reported association between diseases and taster status may be due to chance associations; there are several instances of an initial report and one or more subsequent failures to replicate. In these cases, differences between studies in the characteristics of subjects or low statistical power may explain discordant results. Also, genetic association studies are prone to false positive results due to population stratification, which may be present in some but not all study populations. Finally, the associations may be genuine and may occur either because the taster locus is in linkage disequilibrium with other loci that predispose to a disease, or because the PTC locus has pleiotropic (more than one) effects, or because the disease process changes PTC taster status.

The physiological significance of this sensory polymorphism is not known, but several lines of evidence are consistent with an important role in evolutionary fitness. The high frequency of the trait in many human populations has led to the speculation that PTC insensitivity is a balanced polymorphism. A balanced polymorphism occurs when natural selection favors heterozygotes over both homozygotes. It accounts for the persistence of an allele, e.g., the PTC-insensitive allele, even though it may be deleterious when homozygous.

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Another line of evidence suggests that the PTC sensory polymorphism may have biological significance. In some species, individuals differ in their sensitivity to these taste compounds: primates (62–64), cats (65), and fruit flies (66). The presence of this polymorphism in diverse species suggests that it may have a role in basic physiological processes found in both insects and mammals.

Phenylthiocarbamide (PTC) and PROP are potent antithyroid agents, and more than 1000 research studies on their effects on endocrine function have been reported. Some staple foods contain high levels of bitter thyroid toxins (isothiocyanates, thiocyanates, and other PTC-like compounds), and humans can face the trade-off between having a healthy thyroid axis and obtaining enough calories to survive. Since these compounds act as thyroid toxins by limiting the amount of iodine available for thyroid metabolism, people living in areas with little iodine in the soil are more vulnerable to their effects than those living with a surplus of iodine. The balance between thyroid health and calories is crucial for infants and children since insufficient levels of thyroid hormone during development result in neurological damage, but intake of too few calories results in starvation and death. Differences in taste acuity may have arisen to optimize fitness under conditions of high and low iodine availability and the presence of high or low concentrations of thyroid toxins in staple foods. Many studies have reported differences in food preference as a function of PTC or PROP sensitivity, and some but not all investigators report effects for bitter foods (e.g., Refs. 67–69) (reviewed in Refs 70,71).

In addition to affecting endocrine function, derivatives of these compounds interfere with viral replication (72) and therefore may be important agents in prevention of the spread of infectious disease. In addition, PTC functions as an insecticide, and several species of fruit flies are resistant to its effects. This resistance is heritable, and its genetic location has been mapped (73). If taste sensitivity predicts pharmacological drug effects, as some investigators have suggested (74), then this sensory polymorphism may be a marker for differences in the metabolism of PTC and related compounds (75). Perhaps those individuals that cannot taste PTC are less sensitive to its pharmacological effects.

There is a range of phenotypes associated with PTC status, and it is hard to accept, given the breadth of reported effects, that all are a direct result of genotype at one or a few genes (76). For example, in one study, adult intelligence, food dislikes, smoking, gastric ulcers, Down syndrome (trisomy 21), hypertension, and cystic fibrosis are associated with PROP sensitivity (77). There may be several reasons, however, for these multiple associations. Some results may be spurious. Sensitivity to PTC is an easy

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phenotype to measure and widely used by many investigators. Therefore, some relationships are expected to occur by chance.

The second possibility is that some of these relationships are due to multiple effects of the PTC gene. If the PTC gene(s) is expressed in nontaste tissues, it may participate in other physiological processes. Were this the case, then effects in other organ systems would be expected. For instance, if an allele in a PTC gene led to differential function of the thyroid axis, then effects on growth, metabolism, and reproduction would be an anticipated outcome.

A third explanation is that traits may be associated with PTC as a result of population stratification. To illustrate this concept, imagine one human population in which all members have blue eyes and are sensitive to PTC whereas another population has brown hair and is insensitive. If these two populations intermarry, the offspring with blue eyes are more likely to be sensitive, because these traits occurred together in their recent ancestors, but not because blue eyes and taste sensitivity resulted from alterations in the same gene. Population stratification is a possible explanation for PTC–trait relationships found in some populations but not replicated in others.

A fourth explanation for the relationship between PTC status and other traits is that the gene for a given trait is located near a PTC gene on the same chromosome. In other words, PTC status and the trait may co-occur because these phenotypes do not independently segregate during meiosis.

In summary, many traits are related to PTC status and the identification of the gene or genes that contribute to this sensory polymorphism will provide us with more information about its biological effects. If this polymorphism affects the thyroid axis, then widespread effects on physiological function would be likely.

III. 6-*n*-PROPYLTHIOURACIL AND PHENYLTHIOCARBAMIDE TASTE SENSITIVITY IS INHERITED BUT NOT AS A SINGLE RECESSIVE GENE

After the discovery of the PTC sensory polymorphism, several investigators reported that insensitive parents produced insensitive children, and in families in which both parents were sensitive, a quarter of the children were not (78,79). This observation led scientists to suggest that this ability was inherited as a two-allele trait, with a recessive insensitive allele (often

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abbreviated *t*) and a dominant sensitive allele (often abbreviated *T*). Because the mode of inheritance appeared to be Mendelian and because the trait is easy to assess in the field and classroom, PTC insensitivity is viewed by many as a textbook example of a recessive trait.

Results of some subsequent family and twin studies were consistent with this interpretation of PTC genetics (80–83). Other investigators, however, found that this model of inheritance did not adequately explain their data and suggested other models, such as multiple alleles (84–86), multiple loci (87), and incomplete dominance (6,88,89). In addition, genetic background and environmental modifiers also may have an influence on the phenotype (87,90–92). Genetic variation in fungiform papillae number may account for some variance in PROP sensitivity (6,93) as well as perceived intensity of other taste compounds such as sucrose and salt (94).

Assuming that the trait is Mendelian recessive, as originally hypothesized, we would expect that insensitive parents would be homozygous for the *t* allele and that all children produced should be insensitive to PTC: i.e., they would have the *tt* genotype. However, when all family studies are examined, using PTC thresholds as the phenotype, almost 20% of the offspring of insensitive parents can taste PTC at low concentrations (Table 1). Therefore, it is unlikely that the trait follows a single-gene recessive inheritance pattern.

Table 1 Number of Phenylthiocarbamide-Sensitive Children of Phenylthiocarbamide-Insensitive Mothers and Fathers[a]

Reference	*N* Sensitive children	*N* Total children	PTC-sensitive children, %
(87)	14	38	37
(78)	0	17	0
(126)	3	9	33
(80)	5	26	19
(127)	0	22	0
(128)	0	2	0
(82)	4	26	15
Total	26	140	Average = ~20%

[a] All family studies of phenylthiocarbamide thresholds were identified from a 2001 review article (76), and the numbers of families and offspring were identified. The classification of PTC status varied from study to study, and no effort was made to equate the definition across studies.

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The results of two family studies provided evidence that the taste detection threshold for PTC is a polygenic trait: in one study, a two-locus model was suggested (87), whereas in the other study, a single-gene model with substantial polygenic influences was suggested (92). New models such as the triallelic inheritance pattern described for Bardet-Biedl syndrome could account for the segregation pattern in human families (95).

Initial efforts were made to map the PTC gene by using linkage studies. Linkage studies are undertaken to identify the causal gene or genes responsible for a given genetic trait. Any two siblings share, on average, half their genetic material and at a particular location on a chromosome may share, one, or two alleles inherited from their parents: one allele from the mother and one from the father. When siblings alike in a trait share alleles at a particular region at a greater than chance frequency, this is known as *linkage*.

Early linkage studies assumed that PTC insensitivity was a recessive Mendelian trait (96–108). One locus gave evidence for linkage (Kell) (101,109). However, another study designed to test this linkage relationship did not replicate this finding (110). The reason for this lack of replication is puzzling since similar methodology was used both to phenotype and to genotype family members.

To resolve the discrepant findings of these previous studies, we undertook a linkage study. In this study, we did not make assumptions about the mode of inheritance of the trait and used highly polymorphic markers rather than blood group antigens. A polymorphic marker is a specific locus in the genome where people differ: i.e., the deoxyribonucleic acid DNA sequence varies among individuals. We used highly polymorphic markers because early linkage studies used markers with few alleles at a given genetic location, and therefore determining allele sharing could be difficult. For instance, if both parents had identical genotypes at a particular locus, then it would not be possible to determine allele sharing among siblings (Fig. 1). By using highly polymorphic DNA markers, the specification of allele sharing among siblings is more accurate.

In the linkage study we undertook, we also assumed that the taste trait was quantitative rather than qualitative. We made no attempt to classify people into categories, e.g., tasters and nontasters, but rather used the rating of intensity as the phenotype of interest. The values on the scale ranged from 0 to 100.

To measure taste sensitivity, we chose to use PROP rather than PTC. In recent years PROP has replaced PTC because it is less toxic and does not have a sulfurous odor compared to PTC. Because PROP is used

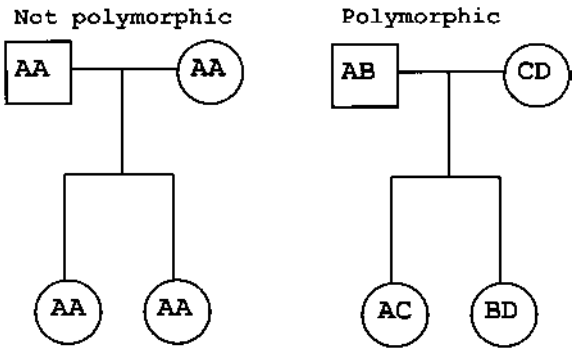

Figure 1 Example of a deoxyribonucleic acid (DNA) marker that is not polymorphic compared to a DNA marker that is highly polymorphic. If there are few alleles of a gene, then, by chance, some mating types will be uninformative; e.g., in this example (left) both parents are homozygous for allele A. The allele sharing between the siblings cannot be specified with certainty. However, when DNA markers are more polymorphic, i.e., there are more alleles with high frequency in the population, parents are more likely to have informative genotypes. In the example to the right, allele sharing between siblings can be specified exactly: i.e., siblings share no alleles at this locus in common. A = allele A, B = allele B, C = allele C, D = allele D.

as a medication to treat Graves' disease, more is known about its properties. When we decided to use PROP as a substitute for PTC we were guided by the studies in the literature that suggested that both traits were equivalent and determined by the same gene or genes. This assumption may have been incorrect, and its impact on the results and interpretation is discussed later.

IV. BITTER RECEPTORS WERE DISCOVERED NEAR THE 6-*n*-PROPYLTHIOURACIL AND PHENYLTHIOCARBAMIDE LINKAGE PEAKS

One genome scan, for PTC threshold, indicates a locus on human chromosome 7 was responsible for the trait, and one genome scan, for PROP sensitivity, indicated that two loci were involved, one on chromosome 5 and one on chromosome 7 near the PTC linkage (Fig. 2). By using the genomic positions suggested by the linkage studies, a family of putative bitter receptors was identified by searching the newly sequenced human genome

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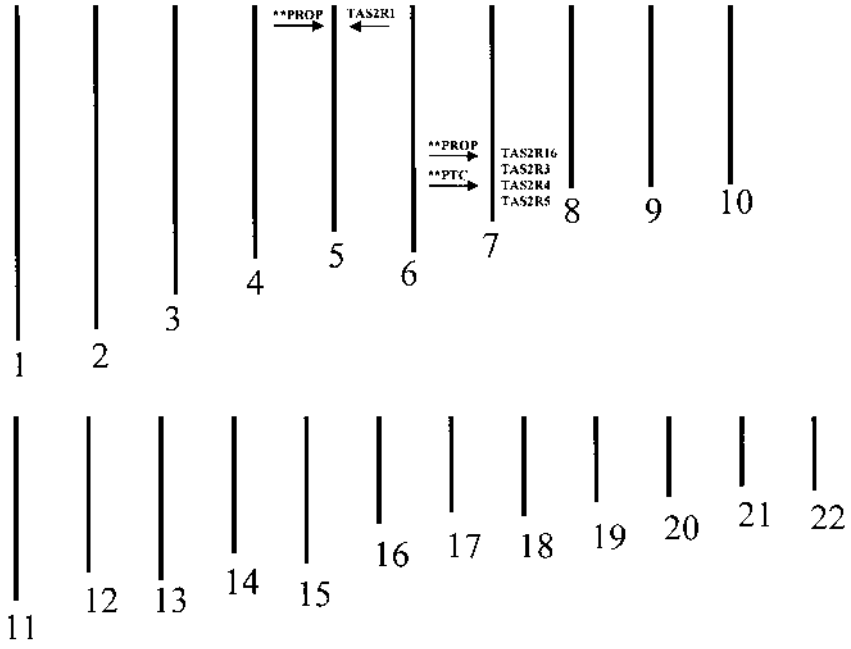

Figure 2 Results of genome scans suggest that bitter receptors are candidate genes. The two regions identified in scans are given to the left of each human chromosome, and the bitter receptor near each linkage peak is shown to the right. There are only three known bitter receptor clusters, those shown on chromosome 5 and 7 and another cluster on chromosome 12. Note that the PTC gene is near the bitter receptor cluster on chromosome 7. PROP = propylthiouracil sensitivity locus; PTC = phenylthiocarbamide sensitivity locus; TAS2R1 = taste receptor, family 2, receptor 1; TAS2R16 = taste receptor, family 2, receptor 16; TAS2R3 = taste receptor, family 2, receptor 3; TAS2R4 = taste receptor, family 2, receptor 4; TAS2R5 = taste receptor, family 2, receptor 5.

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(111–113). One receptor, TAS2R1*, was located near the PROP linkage peak on chromosome 5p15, and another group of bitter receptors was found near the PROP and PTC linkage peak on chromosome 7. Because there are few bitter receptors (especially compared with the olfactory receptor families) and they are found in the only two areas of linkage suggested from studies of PROP and PTC, there is a strong presumption that alleles in one or more of these receptors account for the PROP and PTC phenotype.

The hypothesis that PTC threshold is due to alleles of a bitter receptor has received strong support. One receptor, TAS2R38 on chromosome 7, contains three alleles that form two major haplotypes (A49P†, V262A, and I296V; A-V-I and P-A-V). A haplotype is a set of closely linked genetic markers that tend to be inherited together and are not easily separated during meiotic recombination. For the TAS2R38 gene, a person who has an alanine at amino acid position 49 rather than a proline (A49P) is more likely to have the nontaster haplotype, in other words, also to have a valine at position 262 and an isoleucine at position 296.

This haplotype of three variant sites accounts for 50%–85% of the variance in PTC detection threshold sensitivity (114). Whether alleles of this gene account for other aspects of the PROP and PTC sensitivity (i.e., thresholds and suprathreshold intensity ratings) is not known. However, because 25% of people with the nontaster haplotype (A-V-I) are tasters, the authors concluded that other genes that also partially account for PTC sensitivity exist. Furthermore, only 40% of families demonstrate linkage to chromosome 7, as is consistent with polygenic inheritance (115). Other genes on chromosomes 1, 3, 5, 10, and 16 appear to influence PTC sensitivity but are less prevalent and less potent in the determination recognition threshold (115).

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*The nomenclature for these genes is as follows: TAS denotes a taste receptor gene. The family number follows this designation, which, for the putative bitter receptors, is family 2. R is an abbreviation for receptor, and the final number represents the numerical name of the receptor; hence TAS2R1 is the first receptor of the putative class of bitter taste receptors. Note that other nomenclature, such as TRB or T2RX, is sometimes used in the literature.

†When DNA sequence variants occur in protein coding regions of genes, they often are denoted by the following nomenclature: the more common amino acid, the amino acid position, and the less common amino acid. For instance, A49P indicates that alanine at amino acid 49 is changed to a proline.

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V. 6-*n*-PROPYLTHIOURACIL AND PHENYLTHIOCARBAMIDE INSENSITIVITIES MAY NOT SHARE IDENTICAL GENETIC ARCHITECTURE

Because PROP and PTC are chemically related, initially researchers concluded that someone who cannot taste PROP also cannot taste PTC (116). Therefore, it was assumed that alleles of a single gene accounted for both phenotypes (e.g., Ref. 117). We began our experiments assuming that phenotypes obtained with PROP were equivalent to those obtained with PTC, but this assumption may be wrong. Although the correlation between sensitivity to PTC and PROP among subjects is high, the two phenotypes are not identical; correlations between phenotypes range from 0.69 (118) to 0.84 (117). This lack of perfect correspondence could be due to different sensory qualities of the compounds (which adds noise) or to overlapping sets of genes.*

The sensory qualities of PROP and PTC do differ: PTC has an odor in addition to its bitter taste; that is one reason investigators switched to PROP and away from PTC as a taste stimulus (120,121). In addition, PROP has a more pronounced aftertaste than does PTC (122). It is unclear, however, how important these differences might be to the primary phenotype.

Other evidence suggests that different genes may contribute to PTC sensitivity and PROP sensitivity. When the function of bitter receptors was assayed in cultured cells, one of the bitter receptors tested responded to PROP but not to PTC (112). To the extent that the in vitro function of modified bitter receptors reflects their function in the body, this finding suggests that PROP and PTC do not stimulate exactly the same receptors. In the second case, a genome scan for PROP sensitivity in mice suggested that PROP sensitivity is a polygenic trait determined by at least five genes (123).

Although PTC is the classic example of individual variation in taste perception, there may be other compounds for which people differ in threshold detection or perceived intensity. Bitter receptors have been described and annotated in the human genome (Table 2), and these receptors cluster together with pseudogenes (124). Taste and olfactory receptors may have in common a high degree of polymorphism within

*Repeated measures of PTC thresholds from one person are not identical, and therefore some difference in PTC and PROP phenotypes within an individual could be due to the variation observed with repeated testing (119).

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Table 2 List of Bitter Taste Receptor Genes Identified in Humans (as of June 2003)

Gene name	Accession	Chromosome
TAS2R1	NM_019599	5
TAS2R16	NM_016945	7
TAS2R3	NM_016943	7
TAS2R4	NM_016944	7
TAS2R5	NM_018980	7
TAS2R38/PTC	**AF494231**	**7**
Sim. T2RP25	XM_069625	7
TAS2R39	AF494230	7
Sim. T2RP24	XM_069626	7
TAS2R40	AF494229	7
Sim. T2RP27	XM_095001	7
TAS2R41	AF494232	7
TAS2R7	NM_023919	12
TAS2R8	NM_023918	12
TAS2R9	NM_023917	12
TAS2R10	NM_023921	12
TAS2R13	NM_023920	12
TAS2R14	NM_023922	12
TAS2R50	AF494235	12
TAS2R49	AF494236	12
TAS2R48	AF494234	12
TAS2R44	AF494228	12
TAS2R47	AF494233	12
TAS2R46	AF494227	12
TAS2R43	AF494237	12
Sim. T2RP9	XM_090424	12
TAS2R45	AF494226	12

Sim. similar to: The Phenylthiocarbamide (PTC) gene (TAS2R38) is shown in boldface. Sometimes genes receive a temporary name such as "similar to a known gene" as a placeholder until a permanent name is established. Accession numbers, middle column, are the unique identifying numbers given to deoxyribonucleic acid (DNA) sequences archived in GENBANK, a repository of DNA sequence data (http://www.ncbi.nlm. nih.gov/).

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pseudogenes such that an inactive gene in one person may be active in other individuals (125). These types of sequence variants would be candidates for alleles that contribute to variation in taste sensitivity.

VI. FUTURE DIRECTIONS IN TASTE GENETICS

One goal of future studies is to understand the extent to which alleles of TAS2R38, the PTC gene, relate to the perceptual experience of other bitter compounds, especially PROP. The ability to relate genotype to phenotype will then allow us to understand how other factors, such as sex, experience, and disease, influence this trait and to uncover most or all genes important in gustatory perception.

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3

Assessment of Different Methods for 6-*n*-Propylthiouracil Status Classification

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I. INTRODUCTION

Individual differences in sensitivity to the bitterness of phenylthiocarbamide (PTC) and 6-*n*-propylthiouracil (PROP), which are genetically determined, have been well documented in the literature and reviewed elsewhere in this volume. An individual who does not perceive PTC and PROP as bitter is referred to as a *nontaster* (NT) and one who does as a *taster* (T). More recently, the taster group has been further subdivided into medium tasters (MTs) and supertasters (STs), the latter group comprising individuals who are most sensitive to the bitterness of PTC/PROP (1).

Since the discovery of this genetically mediated sensitivity to the bitterness to PTC/PROP taste researchers have been trying to unravel

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what relationship, if any, exists between PTC/PROP status and sensitivity to other taste stimuli. Review of the literature reveals a continuum of research findings with results that offer compelling support for both ends of the spectrum. Some studies have linked this genetic variation in sensitivity to PTC/PROP to differences in taste perception (2–5), trigeminal irritation (6–8), food preferences (9–12), as well as to dietary intake (13,14). Others have found no such relationships (15–21).

No doubt, there are many reasons that could and do contribute to the inconsistencies seen in the results from PTC/PROP research. However, one that clearly stands out is lack of a standardized method for measuring PTC/PROP sensitivity and approach to the way PTC/PROP individuals are classified into the different PROP status groups. At a minimum, standardized classification methodology would allow a fair comparison of results across different research studies. Researchers have used a variety of measurement methods, ranging from measurement of PTC/PROP threshold (4,9,15,16,18,21) to scaling of different suprathreshold concentrations of PROP solutions. Within the latter approach, researchers have used a variety of intensity scales including magnitude estimation (22), labeled magnitude scale (5,23–25), 15-point line intensity scale (11), as well as 9-point (18,19,26) and 16-point category scales (20). Researchers have also varied in the number of PROP concentrations they use, from five (11,18,22), to three, to one (5,8,23). Some also use reference standards, such as NaCl (4,11,19,20,22,23), sounds (4), and/or weights (27,28) with the assumption that responses to these stimuli are unrelated to PROP status. The data obtained from ratings of control stimuli are typically used either to help establish criteria for separating medium tasters from supertasters (22,23) or to standardize the PROP ratings across subjects in order to minimize differences in scale usage (27). Some investigators have also used filter papers impregnated with suprathreshold levels of PTC or PROP (8,9,29,30).

Additionally, researchers have used different analyses and criteria to establish cutoff values for medium taster, supertaster, and nontaster classifications. For example, some researchers separate medium tasters and supertasters on the basis of the ratio of PROP to NaCl ratings; those who fall below a certain ratio value are classified as medium tasters and those who fall above it as supertasters. However, different researchers have developed their own values, ranging from 1.2- to 2.5 (18,19,24,25). Others, such as Tepper and associates (11,23) and Yackinous and Guinard (20), have used visual classification to segment their subjects into the three PROP status groups by visually comparing their PROP and NaCl psy-

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chophysical functions. Yet others have simply classified their subjects on the basis of the PROP distribution they obtain from their test, defining its two lower and upper extremes as nontasters at one end and supertasters at the other (usually using 25% as the cutoff point), with medium tasters between the two cutoff points (5,8,27).

Few studies report their own test–retest reliability and even fewer compare the reliability of their classification with that of others.Lawless (31) compared four different methods for classifying PTC/PROP tasters and nontasters (subclassification into supertasters was not used at the time) and found a unanimous agreement among all four methods for only 75% of the subjects (though a rank-order correlation between any two methods was higher). Examining the results reported by Ko and collegues (32), we found that they obtained a reliability of 58% between two methods of measurement, magnitude estimation and labeled magnitude scale (LMS), when classifying individuals into nontasters, moderate tasters, and supertasters. Much better reliability was achieved by Tepper and associates (23), who looked at test-retest reliability of one- and three-solution methods as well as reliability across the two test methods. They reported a test-retest contingency coefficient for the one-solution test as 0.69 and for the three-solution test as 0.54. The coefficient of association between the two procedures was 0.74 (87% reliability).

The objective of this set of studies was to compare different measurement and classification methods used in PROP research assessing their within- and between-method reliability. The following three methods were compared: the three-solution (23), one-solution, (23) and a reference method developed at International Flavors & Fragrances (IFF), Union Beach, New Jersey. The data from each method were analyzed in five different ways.

II. ASSESSMENT OF DIFFERENT METHODS OF 6-*n*-PROPYLTHIOURACIL STATUS CLASSIFICATION

A. Background

At International Flavors & Fragrances Inc. (IFF) we became interested in the relation of PROP status to the perception of food, beverages, and oral personal care products. A better understanding of population differences offers us an opportunity to create improved flavors that would be accept-

able to a wide range of individuals irrespective of the differences in their chemosensory status. The initial objective was to classify a large number of individuals into nontasters, medium tasters, and supertasters, using the three-solution method (23); they would then be available for sensory and consumer testing. However, we were unable to classify our population reliably. Upon retesting of the same group of individuals a substantial number of them shifted from one taster status to another. Although this was most common for the medium vs. supetaster groups, it also occurred for the medium taster vs. nontaster group. The same individuals were subsequently retested, using different methods, to see whether retesting would result in a more reliable classification. We found that reliability was a function of two factors: (a) number of PROP solutions used in the test and (b) type of analysis used to establish group status cutoff criteria.

B. Study 1: Three-Solution Test

The three-solution test was first developed by Tepper and coworkers (23). The method was a modification of a five-solution method developed by Bartoshuk (22). In the basic design of the study subjects rate the intensity of three solutions of PROP and three solutions of NaCl (sodium chloride) on a labeled magnitude scale (33). The NaCl is a control solution and is used to aid in classification of the subjects into three taster groups.

1. Methods and Materials

a. Subjects. A total of 194 Caucasian women, recruited from the local area in New Jersey, age 18-55 (37 ± 7), participated in this study. All were healthy, and those who were on medication or were pregnant were excluded from the study. The panelists were informed about the nature of the study and signed a consent form before beginning the study. Panelists were paid for their participation.

b. Stimuli. The stimuli were 0.032 mM, 0.32 mM, and 3.2 mM concentrations of 2 propyl-2-thiouracil (PROP) (Aldrich Chemical, Saint Louis, MO) and 0.01 M, 0.1 M, and 1 M concentrations of NaCl dissolved in spring water, and a blank (water). The stimuli were made by first preparing a stock solution of each taste quality; lower solutions were obtained by diluting the stock solution to the desired concentrations. The PROP solutions were prepared in heated water to improve solubility of the PROP powder.

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c. Procedure. The study was conducted over two sessions with 1-week interval between them. During session 1, all panelists first tasted and rated the three levels of NaCl, followed by the three levels of PROP. During session 2 half the panelists started with NaCl samples and the other half with PROP. This method allowed us to investigate the between-session and stimulus order effects. The presentation of the different stimulus levels within each taste quality was randomized. Subjects were served 10 ml of the taste stimulus, poured into a 1-oz plastic medicine cup, labeled with a three-digit code. The stimuli were at room temperature. During the sip-and-spit procedure subjects first rinsed their mouth with spring water, then placed the entire taste sample in the mouth, swished, expectorated, and rated its intensity. A minimum 1-min interstimulus interval was set, during which panelists rinsed with water as often as necessary. Panelists made their ratings of intensity on a Labeled Magnitude Scale (LMS) (33). The scale was displayed horizontally on a computer screen marked only with verbal labels. They were asked to make their ratings of intensity relative to the strength of all sensations they have experienced in their mouth every day (including varied taste and mouthfeel sensations that arise from hot and cold foods and beverages, spice and spicy foods, toothpaste, mouthwash, medicines, etc.). The data were collected on Compusense direct data entry software (34).

2. Three-Solution Test—Analysis, Results, and Discussion

One of our objectives was to compare test–retest reliability as a function of the type of analysis used to classify individuals. Five different methods were used to analyze these data, and those methods are summarized in Table 1.

The primary method used for analysis was visual classification. Each subject's data from Sessions 1 and 2 were analyzed separately and the subject's taste status across the two sessions was compared. Figure 1 illustrates the group classification of subjects into the three taster groups, nontasters, medium tasters, and supertasters, for each replication. Subjects whose ratings of PROP relative to NaCl were (a) much lower were classified as nontasters, (b) about the same were classified as medium tasters, and (c) much higher were classified as supertasters.

The test–retest reliability was calculated as follows: the sum of the number of subjects classified in the same taster group for both replications, divided by the total number of subjects [here, $(49 + 57 + 33)/194 = 72\%$]. Table 2 summarizes the taster status distribution for Replications 1 and 2.

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Table 1 List and Description of the Five Methods Used to Classify Subjects into Three Taster Groups: Nontasters, Medium Tasters, and Supertasters[a]

Method type	Description of method
25%–50%–25% NT–MT–ST	Subjects classified into taster groups based on the lower and upper 25% of values of distribution
1.2 PROP ratio	Ratio of PROP to NaCl ratings based on two highest concentrations of each [(3.2mM PROP/1M NaCl + 0.32mM PROP/0.1M NaCl)]/2 if Ratio < 0.8 then nontasters if Ratio > 1.2 then supertasters
K-means	Cutoff points on distribution calculated by K-means nonhierarchical cluster analysis on PROP ratings. K-means assignment of cases to fixed number of clusters; PROP ratings forced into three-cluster solution
K-means and ratio	Cutoff points on distribution calculated by K-means nonhierarchical cluster analysis on PROP ratings; panelists who have PROP scores above upper cutoff and PROP ratio above 1.2 classified as supertasters; panelists who have PROP scores below lower cutoff and PROP ratio below 0.8 classified as nontasters
Visual classification	Each subject's data examined individually; subject's PROP function compared to NaCl function; his or her each panelist classified as follows: *Nontaster*: if ratings for PROP much lower than for NaCl *Medium taster*: if ratings for PROP similar to those for NaCl *Supertaster*: if ratings for PROP much higher than for NaCl

[a] NT, nontaster; MT, medium taster; ST, supertaster; PROP, 6-*n*-propylthiouracil.

The test–retest reliability between the two replications was 72% for a three-taster status group classification. The reliability increased to 89% for a two-taster status group classification, that is, when the medium taster and the supertaster data were combined. Averaging ratings across the two sessions the taster status distribution for the three-solution test was as follows: NT = 30%, MT = 44%, and ST = 26%. This distribution re-

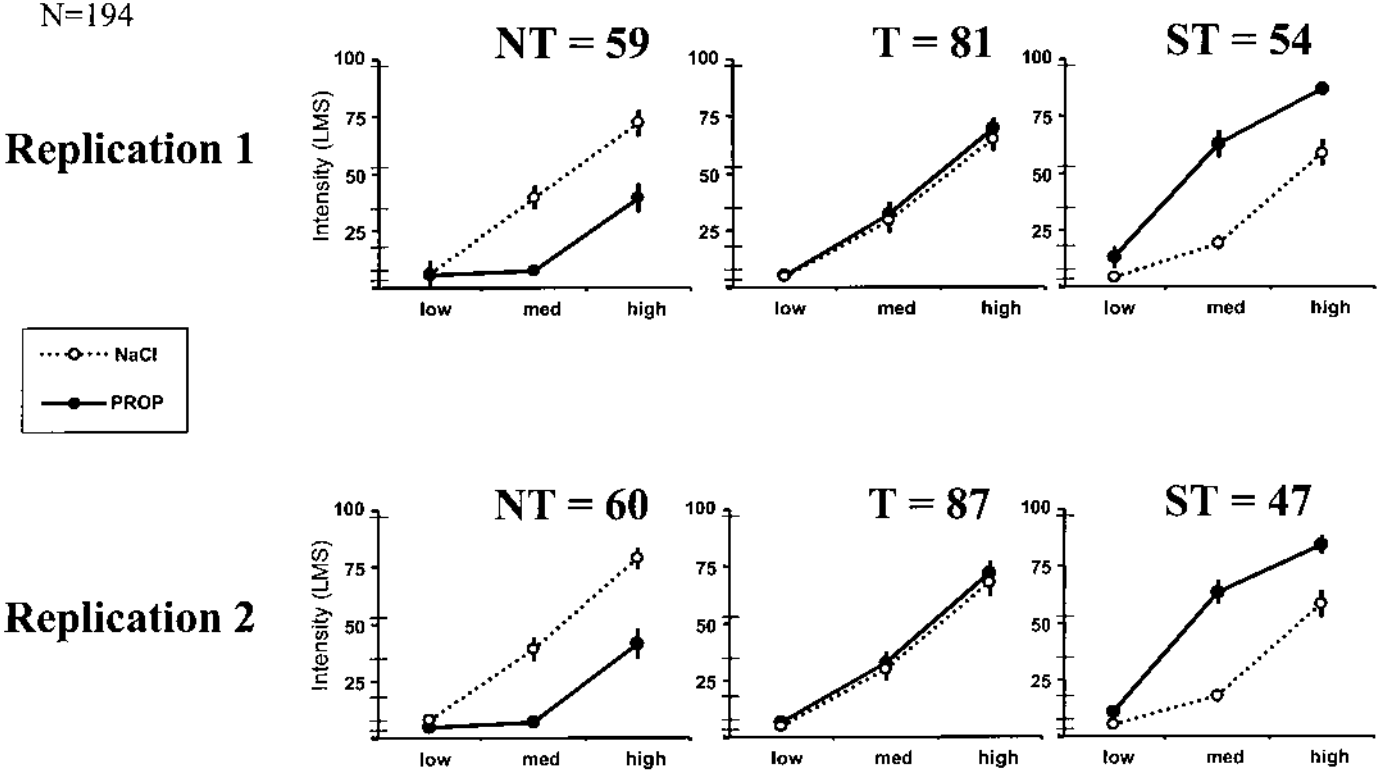

Figure 1 Classification of subjects into three taster groups, nontasters, medium tasters, and supertasters for each replication, based on three-solution test, using visual classification. Subjects who rated PROP relative to NaCl (a) much weaker were classified as nontasters, (b) similar were classified as medium tasters, (c) much stronger were classified as supertasters. NT, nontaster; T, medium taster; ST, supertaster; PROP, 6-*n*-propylthiouracil; LMS, labeled magnitude scale.

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Table 2 Taster Status Distribution for Three-Solution Test for Each Replication[a]

	Replication 1			
Replication 2	Total N = 194	NT = 59	MT = 81	ST = 54
	NT = 60	**49**	11	0
	MT = 87	9	**57**	21
	ST = 47	1	13	**33**

[a] The numbers in the diagonal cells represent those subjects who did not change their taster status from Replication 1 to Replication 2. The remaining cells represent the subjects who changed their taster status. For example, nine subjects who were classified as nontasters on the basis of their data from Replication 1 were classified as medium tasters on the basis of their data from Replication 2, and one changed her status from nontaster to supertaster. The test–retest reliability between Replication 1 and Replication 2 is 72%. Boldface highlights the number of panelists classified in the same taster group in both replicates. NT, nontaster; MT, medium taster; ST, supertaster.

flects the PROP status distribution estimates reported by other researches, for example, Tepper (14,23) and Drewnowski and coworkers (18,19), though it differs somewhat from the distribution reported by Bartoshuk and her collaborators (35).

The same data set was then analyzed using four other methods, and the test–retest reliability values are summarized in Table 3. Visual classification had the highest test–retest reliability, 72%, and was only marginally better than the classification based on a combination of nonhierarchical cluster analysis and 1.2-PROP-ratio method, with a reliability value of 70%. Individually, those two methods had much lower reliability.

Table 3 Comparison of Test–Retest Reliability for Three-Solution Test, as a Function of Type of Analysis Used to Classify Subjects into Three Tasters Groups[a]

Method type	Test–retest reliability
25%–50%–25% NT–MT–ST	54%
1.2 PROP ratio	62%
K-means	63%
K-means and ratio	70%
Visual classification	72%

[a] NT, nontaster; MT, medium taster; ST, supertaster.

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The 25% - 50% - 25% method, which classifies individuals into non- and supertasters on the basis of the extreme ends of the distribution, was least reliable (54%). It should be underscored that though visual classification offered the best reliability, this method is subjective, open to the researcher's interpretation as to what is a "much lower" or "much higher" rating, and requires experience. An inexperienced researcher is less likely to achieve good reliability.

C. Study 2: One-Solution Test

The one-solution test was first validated by Tepper and associates (23) against the three-solution test. In the basic design of the method subjects rate the intensity of only the 3.2 mM solution of PROP and 1 M solution of NaCl. These concentrations represent the middle levels from the three-solution series.

1. Methods and Materials

a. Subjects. A total of 121 women participated in this study. This was a subset of the same women who participated in Study 1. All the panelists from Study 1 were invited to participate in this study, but some were no longer interested or available for testing.

b. Stimuli. The stimuli were 0.32 mM concentration of PROP and 0.1 M concentration of NaCl. The solutions were prepared the same way as in Study 1.

c. Procedure. The same procedure, sample amount, and testing protocol were followed as in Study 1 with one exception: all panelists tasted and rated the NaCl solution first, followed by PROP. There was 1 wk interval between Sessions 1 and 2.

2. One-Solution Test—Analysis, Results, and Discussion

The primary method used to classify subjects was nonhierarchical cluster analysis of PROP ratings. The NaCl data were not used in the classification as they did not improve the reliability of the data. Cutoff values on the LMS were established to determine taster group membership on the basis of the three-cluster solution classification. The distributions of the PROP and NaCl intensity ratings are shown in Fig. 2. As expected, the two distributions look very different. The PROP ratings approximate a trimodal distribution covering the entire scale from No Taste to Strongest

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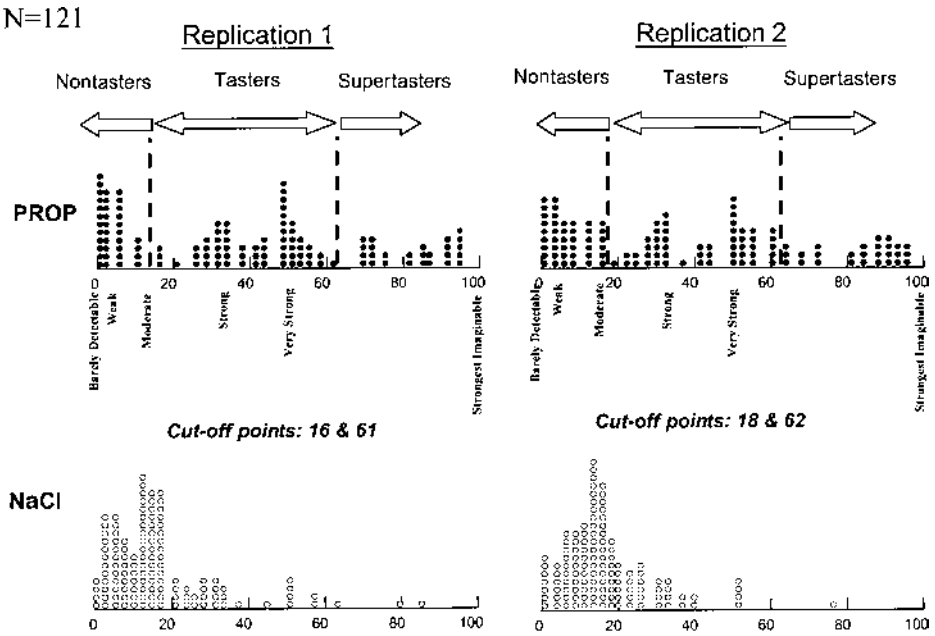

Figure 2 Classification of subjects into three taster groups, nontasters, medium tasters, and supertasters for each replication, based on one-solution test, using nonhierarchical cluster analysis for PROP ratings. The cutoff values on LMS for replication 1 vs. 2, respectively, were 16 and 18 for nontasters and 61 and 62 for supertasters. NaCl ratings for both replications show that the distribution is not trimodal as for PROP. PROP, 6-*n*-propylthiouracil; LMS, labeled magnitude scale.

Imaginable, with cutoff points at around Moderate (16–18 LMS units) for nontaster/medium -taster split and above Very Strong (60–61 LMS units) for medium- taster/super -taster split. The NaCl distribution approximates a unimodal distribution with the ratings centered around the lower end of the scale, ranging between No Taste to around Strong (ca. 35 in LMS units) with only a few exceptions.

The test–retest reliability was calculated in the same way as for the three-solution test, by summing the number of subjects who were classified in the same taster group for both replications and dividing by the total number of subjects [here, (33 + 45 + 21)/121 = 82%]. Table 4 summarizes the taster status distribution for Replications 1 and 2.

Table 4 Taster Status Distribution for One-Solution Test for Each Replication[a]

	Replication 1			
Replication 2	Total N = 121	NT = 36	MT = 58	ST = 27
	NT = 41	**33**	8	0
	MT = 53	2	**45**	6
	ST = 27	1	5	**21**

[a] The numbers in the diagonal cells represent those subjects who did not change their taster status from Replication 1 to Replication 2. The remaining cells represent the subjects who changed their taster status. The test–retest reliability between Replication 1 and Replication 2 is 82%. Boldface highlights the number of panelists classified in the same taster group in both replicates. NT, nontaster; MT, medium taster; ST, supertaster.

The test–retest reliability between the two replications was 82% for a three-taster status group classification. The reliability increased to 91% for a two-taster status group classification when the medium and supertaster data were combined. Averaging across the two sessions the taster status distribution for the one-solution method was as follows: NT = 29%, MT = 49%, and ST = 22%. As before, this distribution reflects the PROP status distribution reported by other researchers (14,18,19,23,35). As for the three-solution test, the data were reanalyzed using four other methods of classification. The reliability data are summarized in Table 5.

Overall, for the one-solution test, the test–retest reliability values were relatively stable across the different methods used. The highest reliability was obtained with the combination of nonhierarchical cluster

Table 5 Comparison of Test–Retest Reliability for One-Solution Test, as a Function of Type of Analysis Used to Classify Subjects into Three Taster Groups[a]

Method type	Test–retest reliability
25%–50%–25% NT–MT–ST	80%
1.2 PROP ratio	78%
K-means	82%
K-means and ratio	83%
Visual classification	82%

[a] NT, nontaster; MT, medium taster; ST, supertaster. PROP, 6-*n*-propylthiouracil.

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analysis and the 1.2-PROP-ratio method (83%) and the lowest with the 1.2-PROP-ratio method alone (78%).

D. Study 3: Reference Test

The method was developed with two objectives in mind: (a) to simplify the testing procedure further and (b) to increase classification reliability further by providing a standard and thus minimizing variability in scale usage.

1. Methods and Materials

a. Subjects. A total of 90 women participated in this study. This was a subset of the same women who participated in Study 1 and/or 2. As earlier, all panelists were invited to participate, but some were not interested or not available for testing.

b. Stimuli. The stimuli were 0.32 mM concentration of PROP and 0.1 M concentration of NaCl. Stimulus preparation followed the same procedure as in the earlier studies.

c. Procedure. As in the previous studies, there were two testing sessions, conducted 1 wk apart. The procedure for both sessions was the same. Panelists were first instructed that the intensity of the Reference sample (NaCl) was set at Moderate level (value 17 in LMS units) and marked on the LMS with a red line labeled *Reference*. This value was obtained by taking the average ratings given to 0.1 M solution of NaCl in our previous studies. Panelists began each session by tasting first the NaCl solution, followed by PROP, with a 1-min interstimulus interval during which they rinsed with water. Subjects were instructed to rate the intensity of the PROP solution relative to the intensity of the Reference solution. The sample amount, the tasting, and the rinsing protocol were the same as in Studies 2 and 3.

2. Reference Test—Analysis, Results, and Discussion

As in the one-solution test the PROP ratings were analyzed by nonhierarchical cluster analysis. Cutoff values on LMS, separating the subjects into three taster groups, were based on three-cluster solution classification. The PROP ratings distribution and cutoff values are shown in Fig. 3.

The test–retest reliability was calculated in the same way as previously, by summing the number of subjects who were classified in the same

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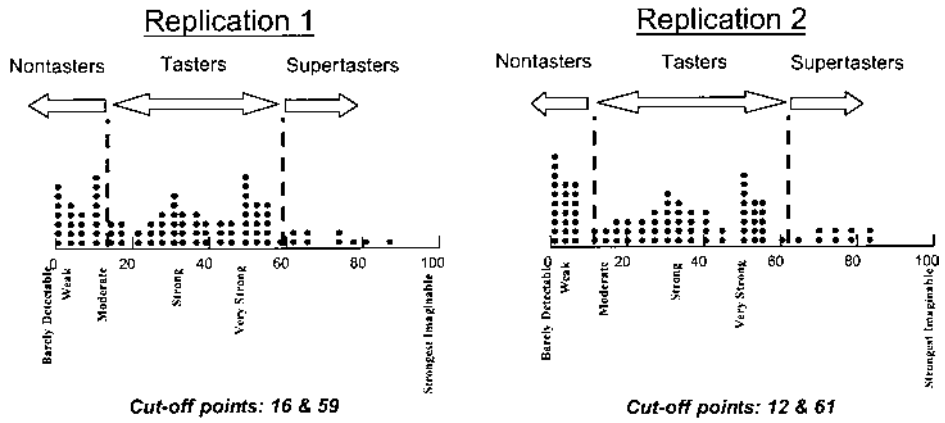

Figure 3 Classification of subjects into three taster groups, nontasters, medium tasters, and supertasters for each replication, based on reference test, using non-hierarchical cluster analysis for PROP ratings. The cutoff values on LMS for Replication 1 vs. 2, respectively, were 16 and 12 for nontasters and 59 and 61 for supertasters. PROP, 6-*n*-propylthiouracil; LMS, labeled magnitude scale.

taster group for both replications and dividing by the total number of subjects [here: (20 + 48 + 6)/90 = 82%]. Table 6 summarizes the taster status distribution for Replications 1 and 2.

The test–retest reliability between the two replications was 82% for a three-taster status group classification. The reliability increased to 89% for a two-taster status group classification when the taster and supertaster data were combined. Averaging across the two sessions the taster status distri-

Table 6 Taster Status Distribution for Reference Test for Each Replication[a]

	Replication 1			
Replication 2	Total N = 90	NT = 25	MT = 56	ST = 9
	NT = 25	**20**	5	0
	MT = 56	5	**48**	3
	ST = 9	0	35	**6**

[a] The numbers in the diagonal cells represent those subjects who did not change their taster status from Replication 1 to Replication 2. The remaining cells represent the subjects who changed their taster status. The test-retest reliability between Replication 1 and Replication 2 is 82%. Boldface highlights the number of panelists classified in the same taster group in both replicates. NT, nontaster; MT, medium taster; ST, supertaster.

Table 7 Comparison of Three-Solution (Visual Classification) with One-Solution Test (K-Means Cluster Analysis)[a]

	Three-solution			
One-solution	Total N = 121	NT = 32	MT = 54	ST = 35
	NT = 35	**27**	8	0
	MT = 59	5	**31**	3
	ST = 27	0	15	**12**

[a] The numbers in the diagonal cells represent those subjects who maintained their taster status from one test to another. The remaining cells represent the subjects whose taster status shifted. The test–retest reliability between the three-solution and the one-solution test is 58%. Boldface highlights the number of panelists classified in the same taster group in both replicates. NT, nontaster; MT, medium taster; ST, supertaster.

bution, for the reference method was as follows: NT = 31%, MT = 60%, and ST = 9%. The percentage of supertasters is small; thus this distribution does not reflect the PROP status distribution as reported by other researchers (14,18,19,23,35). Because of the design of this study, panelists did not rate any samples of sodium chloride; it was therefore not possible to reanalyze the data by using three of the four other methods.

E. Comparison of the Three Test Methods

Tables 7–9 show the between-test methods reliability values. Only the data of those panelists who participated in the two tests being compared were

Table 8 Comparison of Three-Solution (Visual Classification) with Reference Test (K-Means Cluster Analysis)[a]

	Three-solution			
Reference	Total N = 90	NT = 33	MT = 37	ST = 20
	NT = 28	**25**	3	0
	MT = 54	7	**31**	16
	ST = 8	1	3	**4**

[a] The numbers in the diagonal cells represent those subjects who maintained their taster status from one test to another. The remaining cell represent the subjects whose taster status shifted. The test–retest reliability between the three-solution and the one-solution test is 67%. Boldface highlights the number of panelists classified in the same taster group in both replicates. NT, nontaster; MT, medium taster; ST, supertaster.

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Table 9 Comparison of One-Solution (K-Means Cluster Analysis) with Reference Test (K-Means Cluster Analysis)[a]

	One-solution			
Reference	Total N = 72	NT = 22	MT = 36	ST = 14
	NT = 19	**18**	1	0
	MT = 45	3	**34**	8
	ST = 8	1	1	**6**

[a] The numbers in the diagonal cells represent those subjects who maintained their taster status from one test to another. The remaining cells represent the subject whose taster status shifted. The test–retest reliability between the three-solution and the one-solution test is 81%. Boldface highlights the number of panelists classified in the same taster group in both replicates. NT, nontaster; MT, medium taster; ST, supertaster.

used in the analysis. For the three-solution method the reliability was calculated by using the visual classification data, and for the one-solution and the reference methods reliability was calculated by using nonhierarchical cluster analysis data. Comparison of the three-solution method with the one-solution and Reference methods gave the lowest reliability of 58% and 67%, respectively. The low reliability between the methods may, in part, be due to the fact that both the measurement methods and the analysis procedures varied. Conversely, it is perhaps not suprising that the one-solution and reference methods had a fairly good reliability of 81% since those two methods are similar.

F. Discussion

All three testing methods, the three-solution, one-solution, and Reference tests, had one feature in common: two-group classification into nontasters and tasters provided much more reliable data than the three-group classification into nontasters, medium tasters, and supertasters. The three-solution procedure had the lowest test–retest and between-test reliabilities. This procedure also requires the longest administration and data classification periods. Visual classification, which offered the best test–retest reliability (72%), is subjective, and reliability varies with the experience of the researcher. This testing method also suffers from potential carryover effects. For PROP tasters the bitterness of this chemical lingers in the mouth even after a 1-min break between samples and several water rinses. It is possible that the carryover effect may contribute

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to the low reliability scores, especially for the medium tasters and supertasters. Longer interstimulus interval may reduce the carryover effect but also increases the testing time.

Relative to the three-solution test, the one-solution and Reference test methods offer three advantages: they have better test–retest reliability, are much faster to administer, and do not suffer from carryover effects. The two methods are very similar, and the between-method reliability for both was 81%. There was, however, a difference in the PROP distributions obtained by these two methods. The number of supertasters in the Reference method was smaller and the number of medium tasters was larger than would be expected. It is possible that providing an intensity anchor may have had the effect of suppressing the intensity ratings. It is also possible that the low number of supertasters reflected the actual PROP status distribution in the group tested. Compared to the earlier *N* the number of panelists who returned for this test was somewhat lower, and since supertasters find PROP very aversive, they were less likely to return (see Table 6).

G. Summary and Conclusions

Review of the PTC/PROP literature reveals lack of a generally agreed on method for measuring PROP sensitivity and classifying individuals on the basis of their PROP status. Assessment of the three methods showed that both the test–retest reliability and across-test method reliability can be low, depending on the measurement method used and classification methods compared. Nontasters were less likely to be misclassified than medium tasters and supertasters, and classification into two groups, tasters vs. nontasters, yielded higher reliability values than classification into three groups, nontasters, medium tasters, and supertasters.

It is difficult to compare our reliability values with those of other researchers as most do not report them. However, Tepper and associates (23) have reported a reliability of 87% between the one- and three-solution methods, which is considerably higher than the value of 57% reported here. Though in both cases the same methods were used to test PROP sensitivity, somewhat different approaches were used to classify the subjects, especially in the one-solution test. The difference in the reliability values may, at least in part, be related to those differences. Tepper and colleagues (23) classified their subjects by using numerical cutoff scores, which were determined from the label descriptors from the LMS as a guide. Additionally, the sodium chloride ratings were used to help classify some

borderline individuals. Here, nonhierarchical cluster analysis on PROP ratings was used to group individuals into three taster groups. Tepper and associates used more subjective criteria to help classify individuals, particularly in borderline cases, in which a decision was made about the size of the difference between PROP and NaCl ratings. Using strictly statistical criteria, on the other hand, may have misclassified those subjects by not allowing for individual differences in scale usage that may be unrelated to PROP-tasting status.

The size of test–retest reliability scores also varied with methods used, although they were higher than the between-methods reliability values. The scores were higher for the one-solution and Reference methods, and lower for the three-solution test. As suggested earlier, one possible reason for the lower reliability of the three-solution test may be carryover effects, especially for supertasters. It is clear that the measurement of PROP sensitivity remains a complex issue that reflects, as yet, an imperfect understanding of the genetic mode of inheritance of this trait (36). Classification of individuals into three distinct groups may not be the most useful approach if the ability to taste PROP is transmitted as a polygenic trait, as has been hypothesized by Reed and colleagues (see Chapter 2 in this volume). Some researchers have proposed an alternative way of looking at this issue; for example, Bartoshuk and her colleagues began to treat the PROP distribution as a continuum (see Chapters 1 and 10 in this volume).

III. 6-*n*-PROPYLTHIOURACIL STATUS AND THE PERCEPTION OF OTHER ORAL STIMULI—PILOT STUDIES

Despite some of the problems encountered while trying to classify our subjects into one of the three PROP taster groups, we were still interested in pursuing the original goal of investigating the relationship between PROP status and the perception of other tastes/flavors. Two studies were conducted; one involved the perception of a personal care product, toothpaste, and the other perception of artificial sweeteners in a cola beverage.

A. Study 1: Toothpaste

Individuals who are PTC/PROP-sensitive have been reported to be more sensitive to bitterness and off-taste of artificial sweeteners (2,4) as well as to

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the irritation of trigeminal stimuli (6–8,11). The objective of this study was to investigate the differences in the ways nontasters and supertasters perceive the flavor of toothpaste. The hypothesis was that supertasters would be more sensitive than nontasters to the bitterness, cooling, and burning/biting/tingling sensations of the toothpaste.

1. Methods and Materials

a. Subjects. A total of 18 of the most reliable nontasters and 17 of the most reliable supertasters participated in this test.

b. Stimuli. The stimulus was a U.S. market toothpaste, containing baking soda and peroxide.

c. Procedure. All panelists participated in two sessions. The first session consisted of training, and the second, evaluation of the toothpaste. During training the panelists smelled and tasted the toothpaste and discussed the key sensory attributes. To help them better differentiate between the sensation of Cooling and the perception of the olfactive note Mintiness the panelists tasted a 0.1% solution of peppermint with their nostrils open and closed.

For quantitative evaluation, instead of rating the intensity of each attribute on a scale, the panelists were trained to indicate the percentage (0%-100%) of each attribute that characterized the total flavor of toothpaste. Panelists did not need to use every attribute presented to them for evaluation. However, the total evaluation had to equal 100%. This approach was adapted from Cowart (37).

During the evaluation session subjects first rinsed their mouth with spring water, then brushed their teeth with the toothpaste for 15 sec on each side of the mouth. Before rinsing they rated Liking of the sample (9-point hedonic scale), Overall Intensity (9-point intensity scale), and relative percentage contribution of the following attributes to the overall flavor: Mintiness, Coolness, Sweetness, Saltiness, Bitterness, Grittiness, Buring/Biting/Tingling, Bad Aftertaste/Off-Taste. All the evaluations, except Liking, were made at six different time points: before rinsing, immediately after rinsing, then 2, 4, 8, and 15 min after rinsing. Liking was rated immediately after brushing and at the 15-min evaluation.

2. Analysis, Results, and Discussion

Analysis of variance (ANOVA) was used to compare nontasters' and supertasters' liking scores for each sample. The intensity ratings and each

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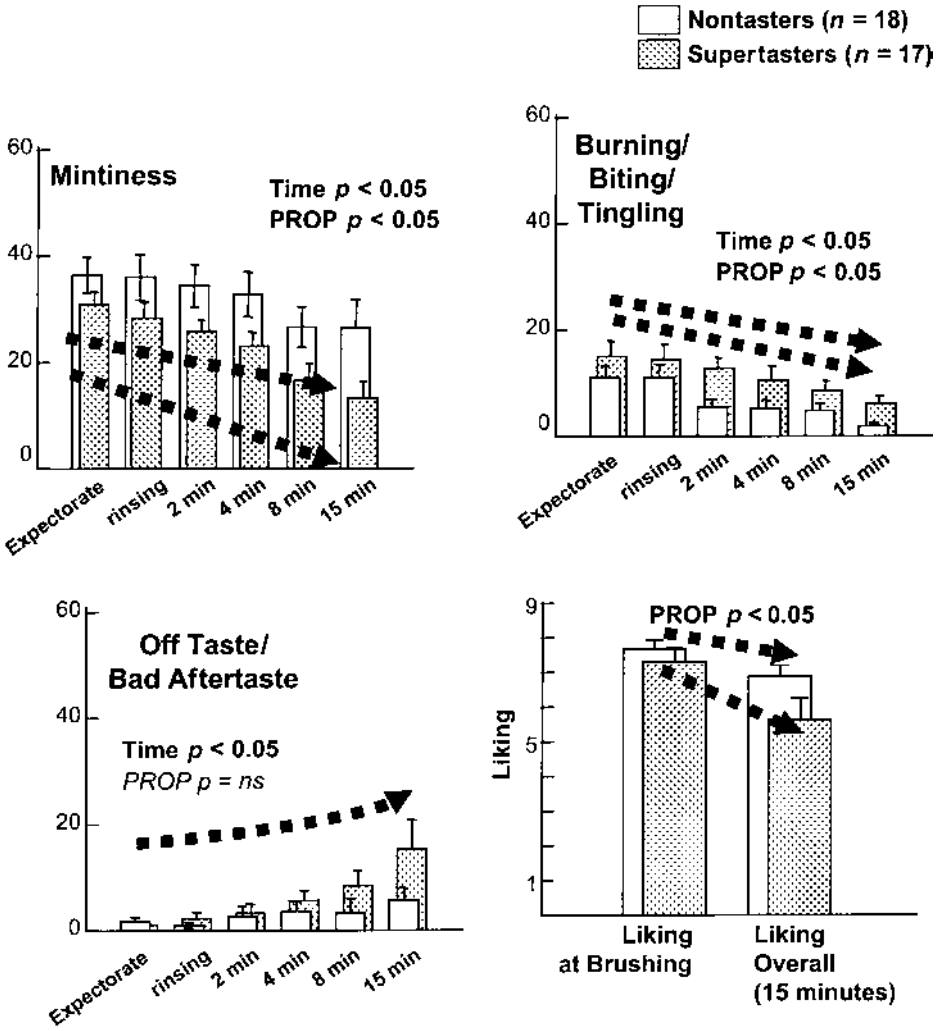

Figure 4 Average ratings of three attributes and liking scores. Supertasters reported a lower perception of mintiness but an increased perception of the Burning/Biting/Tingling and an increase in Off Taste/After Taste. Supertasters also reported a significant decrease in liking of the sample. PROP, 6-*n*-propylthiouracil.

one of the eight attributes were analyzed separately by repeated measures ANOVA, with PROP Status and Time as between- and within-subject factors, respectively. Level of statistical significance was set at $p < 0.05$, and p value between 0.05 and 0.1 was defined as directional or trend.

The key findings are shownn in Fig. 4. There were no differences between the two groups with respect to the relative perception of either Bitterness or Coolness. However, nontasters and supertasters differed significantly in their evaluation of Burning/Biting/Tingling. Thus our hypothesis was partially supported in that supertasters showed more sensitivity to one of the trigeminal sensations. This finding is quite consistent with the results of Karrer and Bartoshuk (6), Bartoshuk and colleagues (7), and Prescott coworkers (8), who have found that supertasters are more sensitive to such trigeminal stimuli as capsaicin, ethanol, and cinnamaldehyde, respectively. No data have been reported on the perception of coolness.

Supertasters also experienced more buildup over time of Off-Taste/Bad Aftertaste. Presumably linked to the increase in Bad Aftertaste are the decreased Liking scores. The decrease of Liking over time was significantly greater for supertasters.

Interestingly, supertasters experienced relatively less Mintiness than nontasters. However, we interpret this result as an artifact of the evaluation method rather than an indication that the two groups vary in their perception of this olfactive note. Because supertasters experienced greater Burning/Biting/Tingling and the total flavor perception equals 100%, the relative perception of another note had to be lower. It is not clear why Mintiness specifically decreased, possibly because it was the only olfactive note present.

B. Study 2: Artificial Sweeteners in a Cola Beverage

Artificial sweeteners such as saccharin and acesulfame-K have been found to have bitter taste and a lingering bitter aftertaste (38,39). The data relating PROP status to sensitivity of bitterness in artificial sweeteners are inconsistent. There is some evidence suggesting that tasters of PROP are more sensitive to the bitterness and off-taste of saccharin, particularly at lower levels (2,4,19). Horne and colleagues (25), on the other hand, found no positive relationship between the perception of bitterness of saccharin and acesulfame-K and PROP status.

The goal of this study was to investigate whether PROP supertasters varied from PROP nontasters in their perception of a cola beverage sweetened with five different artificial sweeteners. We hypothesized that

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supertasters are more sensitive to the bitterness and off-taste of artificial sweeteners.

1. Methods and Materials

a. Subjects. A total of 35 of the most reliable nontasters and 31 of the most reliable supertasters participated in this test.

b. Stimuli. Five different artificial sweeteners were used to sweeten an IFF-made model carbonated cola beverage: high-fructose corn syrup (15.5%), aspartame (0.0416%), saccharin (0.033%), mixture of aspartame and acesulfam-K (0.0208% aspartame and 0.0208% acesulfam-K), mixture of sucralose and acesulfam-K (0.040% sucralose and 0.0133% acesulfam-K). Cola formulation was similar in caffeine, cara- mel color, and other ingredients to a market cola beverage.

c. Procedure. All subjects participated in two sessions. During the first session panelists were given 20-min training and evaluated two of the five cola samples. During the second session they evaluated the remaining three samples.

During the training the panelists were given the opportunity to familiarize themselves with the list of flavor and sensation attributes that they would be evaluating as well as instructions describing the evaluation method. As in the toothpaste study, the quantitative evaluation of the attributes was done by the panelists' indicating the percentage (0%-100%) of each attribute that characterized the total flavor of cola.

During evaluation the panelists first rinsed their mouth with spring water, swallowed it, then tasted and swallowed 30 ml of the cola sample in two consecutive sips. Just after swallowing they rated Liking of the sample (9-point hedonic scale), Overall Intensity (9-point intensity scale), and relative contribution of the following attributes to the overall flavor: Cola flavor, Bitterness, Sweetness, Carbonation, Off Taste/Bad Aftertaste, Other Sensation. All the ratings, except Liking, were made at six different time points: immediately after swallowing, and then 1, 2, 3, 5, and 7 min after swallowing the sample. Liking was rated immediately after swallowing and at the 7-min evaluation. The cola samples were served cold. Subjects had a 5-min break between samples during which they ate a cracker and rinsed their mouth with spring water.

2. Analysis, Results, and Discussion

Analysis of variance (ANOVA) was used to compare nontasters' and supertasters' Liking scores for each sample. Repeated measures ANOVA

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was used to compare NT and ST on (a) intensity scores, (b) changes in proportion of each attribute in each product over time, and (c) cross-product comparison for each attribute at each evaluation time (Samples as the within-subject repeated factor), with PROP status as the between-subject factor in all cases. Level of statistical significance was set at $p < 0.05$; p value between 0.05 and 0.10 was defined as directional or trend.

Overall, our hypothesis that supertasters are more sensitive specifically to Bitter and/or Off Taste/Bad Aftertaste generated by artificial sweeteners was not supported. However, supertasters reported a larger buildup over time of Other Sensation for the two samples containing aspartame. Figure 5 shows the results for the two samples by taster status. A significant difference was also found for sample Overall intensity: supertasters rated all the samples as significantly more intense. There were no significant differences between the two taster groups in evaluation of Bitterness and/or Off Taste/Bad Aftertaste. These results are in agreement with those obtained by Horne and associates (25), though they contradict some of the earlier work on saccharin (2,4,19).

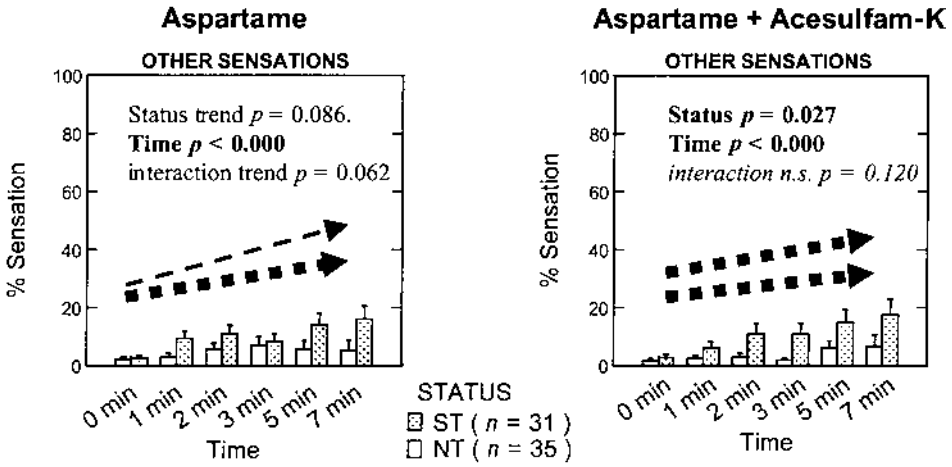

Figure 5 Average ratings of Other Sensation, over time, for two samples containing aspartame, aspartame and aspartame + acesulfam-K, by taster status. Supertasters reported a larger buildup of Other Sensation: directional difference in the sample with aspartame only and a significant difference in the samples with a mixture of aspartame + acesulfam-K. ST, supertaster; NT, nontaster.

It is still possible that the complexity and familiarity of stimuli, such as the cola beverage studied here, may mask the perceptual differences that can be measured more easily when less complex taste stimuli, such as a solution of saccharin, are used. Although the results reported by Horne and coworkers (25) would speak against this hypothesis, the work of Mela (26) offers some support. He found that tasters and nontasters differed in their intensity ratings of suprathreshold concentrations of isohumulone (a bitter substance found in beer) when presented in water but not in beer.

Additionally, it should be acknowledged that the task of identifying and rating several attributes in a product over several periods is quite complex. Although the panelists were given some prior training to help them identify the differentaste and olfactive attributes, they were not trained panelists. The complexity of this task may have, in part, contributed to the insignificant results.

C. Summary and Conclusions

The issue of the relationship between PROP status and sensitivity to other taste and food stimuli remains controversial. Despite our very best efforts to use subjects who were the most reliable non- and supertasters, we still did not find many significant differences between the two groups with respect to the perception of toothpaste or artificial sweeteners presented in a cola beverage on such basic taste qualities as bitterness or sweetness. However, we did find some differences in the perception of trigeminal stimuli for the sensation of tingling/biting/burning but not coolness. The PROP-related differences in the perception of trigeminal stimuli are generally more reliable than those for taste (e.g., 6, 8). It is possible that supertasters perceived the samples differently than nontasters did but, as consumers, could not articulate those differences accurately. This could explain why no significant differences in bitterness were found for any of the products, but supertasters reported more bad aftertaste for toothpaste and higher Overall Intensity and buildup of other sensations for the cola samples containing aspartame.

The PTC-/PROP-related difference seen in solutions of bitter and sweet tastants may also be limited to those simple stimuli and play a relatively minor role in the perception of more complex stimuli such as food. Perhaps most differences between PTC/PROP tasters will be found in nonfood consumer products or unfamiliar food products, with which individuals rely on perception rather than experience.

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IV. CONCLUSIONS

None of the methods currently used in PTC/PROP studies offers optimal reliability and therefore none can be said to provide completely accurate classification. Tepper and colleagues (23) reported 87% reliability for the three-solution vs. the one-solution method and high test–retest reliability of the latter method. The current studies tested a variety of approaches and observed a range of results depending on the method selected. The one-solution test proved more reliable than the three-solution test and achieved ca. 82% reliability when analyzed by K-means cluster analysis. Results were comparable when the NaCl reference standard was used. Thus, the present findings strengthen our understanding of which classification methods are likely to be most useful and which should be avoided.

Finally, to our knowledge, this is one the few studies to examine the relationship between PROP sensitivity and sensory perception of market products. Additional studies will help to determine the usefulness of genetic taste screening for understanding consumer perception and in other industrial applications.

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4

6-*n*-Propylthiouracil Tasting and the Perception of Nontaste Oral Sensations

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I. 6-*n*-PROPYLTHIOURACIL TASTING AND TASTE ANATOMY

The implications of variations in response to the taste of the compounds phenylthiocarbamide (PTC) and 6-*n*-propylthiouracil (PROP) have been investigated for more than 60 years. Yet it is only in the past two decades that this phenomenon has begun to create serious interest among chemosensory psychophysicists. Despite some contradictory and negative findings (see Chapter 11 in this volume), this interest has produced a body of research showing that variations in sensitivity to the bitterness of PTC and, especially, PROP are also associated with variations in sensitivity to other taste compounds—both other bitter compounds and compounds that stimulate other tastes qualities.

Those sensitive to PROP (tasters) have been reported as rating urea, sucrose octa-acetate and denatonium benzoate (1), sodium and potassium

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benzoate, potassium chloride (2), quinine (3), and caffeine (4) as more bitter than do PROP nontasters (NTs), and sucrose as sweeter (5). Both the bitterness and the sweetness of saccharin are rated as more intense by PROP tasters than by NTs (6). There are also reports that the saltiness of NaCl (7) and sourness of citric acid (8) are both positively correlated with PROP ratings. Such taster group differences are especially evident when PROP supertasters (STs) and mediumtasters (MTs) are differentiated. In a recent study (9), STs gave higher ratings than NTs and/or MTs to the saltiness and bitterness of NaCl/QHCl mixtures, the bitterness of sucrose/QHCl mixtures, the sweetness of sucrose/citric acid mixtures, and the saltiness and sourness of NaCl/citric acid mixtures. Similar effects were evident in ratings of the overall intensity of these mixtures, particularly at the higher concentrations of the individual tastants. Sensitivity to PROP also predicted the degree to which individual taste qualities interact with each other in mixtures, e.g., the extent to which bitterness suppressed sweetness intensity (9,10).

This body of research suggests that PROP sensitivity acts as an index of a broader sensitivity to tastes. This presumably occurs because although sensitivity to PROP has been associated with a specific genetic locus, distinct from other taste loci (see Chapter 2 in this volume), variations in sensitivity are also strongly associated with individual differences in taste anatomy.

Miller and Reedy (11) demonstrated in young adults that the density of fungiform papillae on the anterior tongue can vary by as much as 16-fold. Within these subjects, two distinct and nonoverlapping groups varying in density of fungiform papillae, and taste buds and pores within papillae, could be identified. The mean ratings of the intensity of a range of concentrations of sucrose, NaCl, and PROP (but not citric acid and quinine) were shown to be higher in subjects with greater fungiform papillae taste pore densities. Bartoshuk and associates. (12) reported similar significant associations between PROP intensity ratings and density of both fungiform papillae and taste pores. Consistently with this, PROP thresholds were significantly negatively correlated with both papillae and pores, and dividing subjects into NTs, MTs, and STs showed a greater than fivefold increase in taste pore density between NTs and STs. These data suggest strongly that associations between PROP tasting and the intensity of other tastes/tastants may be at least partly mediated by the correlation of PROP intensity with taste pore/papillae density.

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II. SOMATOSENSORY INNERVATION OF "TASTE" STRUCTURES

In addition to innervation by the chorda tympani (cranial nerve VII), carrying taste fibers, the anterior tongue also receives extensive innervation by trigeminal nerve fibers (cranial nerve V), which respond to a range of somatosensory (tactile, temperature, pain) stimuli. In fact, it has been estimated that 75% of the innervation of fungiform papillae is by trigeminal fibers (13), which not only enter the taste bud but also occupy the surrounding epithelium, terminating at the apex of the papilla (14). Chemicals interact with trigeminal free nerve endings via both the taste pore and the pathways in the epithelium surrounding the taste bud. In addition to polymodal nociceptors responsive to noxious stimuli (both chemical and

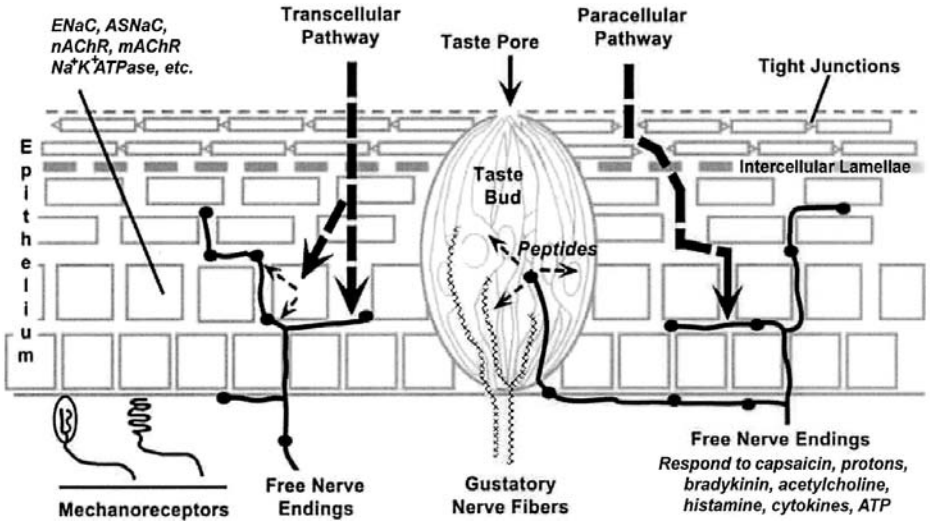

Figure 1 Schematic of the innervation of taste buds and surrounding epithelium showing different trigeminal fiber types (mechanoreceptors and free nerve endings) their relationship to the taste bud, and pathways for chemical activation of these fibers. ENaC, epithelial sodium channel; AsNaC, amiloride-sensitive sodium channel; nAChR, nictinic acetylcholine receptor; mAChR, muscarinic acetylcholine receptor; Na^+K^+ATPase, sodium-potassium adenosine triphosphatase; ATP, adenosine triphosphate. (From Ref. 15. This figure is used by permission of John Wiley & Sons, Inc.)

heat), other trigeminal fibers are sensitive to warmth and cooling, and mechanoreceptors respond to tactile stimulation (15). Figure 1 is a schematic of a taste bud and epithelium showing the coexistence of chorda tympani and trigeminal fibers, both within the taste bud and in the surrounding epithelium.

The intensity of tastants applied to the anterior tongue is a function of area, and therefore number of fungiform papillae, stimulated (16). Given the extensive innervation of fungiform papillae by trigeminal fibers, it could be expected that the intensity of trigeminally mediated qualities would also be a function of number of fibers activated. Such sensations are, of course, relatively commonplace and include the irritation and burning produced by spicy foods, the cooling produced by menthol, the bite of alcohol and acids, and the temperature and tactile properties of foods and beverages generally (17) (see later discussion). Because of the positive association between PROP ratings and fungiform papillae and pore density, PROP taster groups should also be expected to vary in their perception of such trigeminally mediated sensations.

III. 6-*n*-PROPYLTHIOURACIL TASTING AND THE BURN OF CAPSAICIN

Capsaicin is the primary irritant found in chilis and has become the most common compound used in studies of oral irritation (17,18). The oral burn of capsaicin is thought to be mediated by polymodal nociceptors, primarily within trigeminal fibers (19,20). Research on the burn of capsaicin has provided strong evidence that sensitivity to PROP is also associated with nontaste (that is, somatosensory) oral sensations. In the first investigation of this relationship, Karrer and Bartoshuk (21) found that the magnitude estimates of PROP NTs were lower than those of tasters for a range of capsaicin concentrations (10–1000 ppm) applied to the anterior tongue both before and after densensitization to capsaicin burn (during which trigeminal fibers are relatively insensitive to further stimulation with capsaicin and some other irritants). Similar findings were reported by Tepper and Nurse (22), who measured oral burn ratings of NTs, MTs, and STs for capsaicin in the 10- to 100-ppm range applied to the anterior tongue. The PROP group differences were strongest at the highest concentrations in both of these studies (Ref. 21: 100 and 1000 ppm; Ref. 22: 50, 75, 100 ppm). Subsequent research using whole mouth stimulation with 3-ppm capsaicin solutions also found that PROP NTs rated burn intensity lower than did

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tasters (23). It should be noted, however, that such whole mouth stimulation provides much higher effective burn than application of the equivalent concentration to a limited area on the anterior tongue.

This research was extended by Snyder and colleagues (24), who also distinguished ST and MT groups. The STs were found to rate the burn of 100 ppm capsaicin applied to the anterior tongue as more intense than did either MTs or NTs. Similar effects were found when the stimulus was a capsaicin-impregnated candy (25). In addition, Bartoshuk and coworkers (25) found sex and age differences in burn perception; with the highest burn ratings were made by older female STs.

Some of these studies (21,22) have indicated that the strength of the relationship between PROP ratings and those of capsaicin burn is dependent on the concentration of the stimulus. This is supported by the more recent data in Fig. 2, which illustrate the relationship between ratings of PROP bitterness and capsaicin burn at 1, 10, and 100 ppm on the labeled magnitude scale (LMS) (26).

There are also data showing that this relationship is dependent upon the location of the stimulation by the irritant. By comparing the responses of PROP NTs and tasters to capsaicin burn on both the dorsal (containing taste papillae) and ventral (no papillae) surfaces of the anterior tongue, Karrer (27) found that the relationship between intensity of oral burn and PROP status holds only at sites possessing taste papillae. These data, therefore, strongly support the explanation that the differences in responses to oral irritation, as a function of differences in PROP sensitivity,

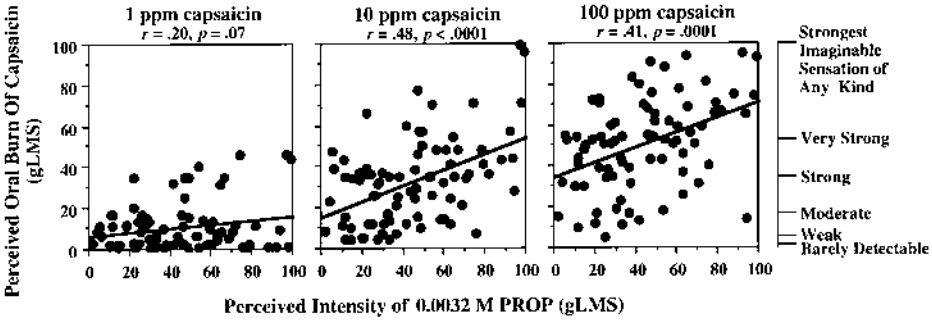

Figure 2 Relationship between ratings of the bitterness of 0.0032M PROP and the oral burn of capsaicin across increasing concentrations (1, 10, 100 ppm). gLMS, general labeled magnitude scale; PROP, 6-*n*-propylthiouracil.

are determined by the underlying variations in papillae density. Moreover, as might be expected, ratings of capsaicin burn are also significantly correlated with density of fungiform papillae on the anterior tongue (26).

IV. OTHER IRRITANTS

In addition to capsaicin, Prescott and Swain-Campbell (23) compared PROP NT and taster responses to the irritation of cinnamaldehyde, the pungent compound in cinnamon, and ethanol, both presented as a series of whole mouth solutions administered at the rate of one solution/min. In both cases, there were large overall differences in intensity ratings between the tasters and the NTs, who gave lower ratings. One of the aims of this experiment was to determine whether individual differences in the degree to which increases (sensitization) or decreases (desensitization) in irritation intensity occurred with repeated stimulation could be explained by variations in PROP sensitivity. However, both groups showed an equivalent degree of desensitization.

A number of other studies have compared PROP taster groups in their responses to ethanol (26,28,29). Bartoshuk and colleagues (28) found that STs rated both bitterness and irritation from 10% alcohol applied to tongue tip as stronger than did MTs and NTs. Irritation ratings of a range of ethanol solutions varying from 30% to 70% applied bilaterally to the anterior tongue were all found to be significantly correlated with PROP ratings (26). The r values ranged from 0.386 to 0.546, but with no obvious increase with ethanol concentration, showing that, in contrast to associations between PROP and capsaicin, the magnitude of this association was not strongly related to ethanol concentration.

V. TACTILE SENSATIONS

Trigeminal fibers also contain mechanoreceptors that occupy fungiform (and other) papillae, although not within the taste buds themselves (14), and respond to tactile stimulation (see Fig. 1). Stimulation of mechanoreceptors may underlie a variety of common oral sensations, including viscosity, creaminess, fattiness, and many other textural qualities in foods and beverages.

Prutkin (26) reported positive correlations between PROP ratings and ratings of the viscosity of 10% ($r = 0.344$) and 100% ($r = 0.472$)

canola oil. At these same concentrations, there were also significant correlations of PROP ratings with counts of fungiform papillae (r = 0.339 and 0.235, respectively), again implicating intra-individual variations in papillae density as the source of relationship with PROP intensity. A similar study was conducted with solutions of guar gum varying in viscosity (six concentrations from 0.1 to 1.0 g/ml) (26). These data are shown in Fig. 3. Positive relationships with PROP ratings were evident at the four highest concentrations.

The quality of astringency has been shown to arise from reduced oral lubrication that follows the precipitation of salivary proteins, commonly an effect of tannins in foods and beverages (30). Astringent sensations, including drying, roughing, and puckering (31), presumably reflect activation of mechanoreceptors throughout the oral cavity. Such a generalized effect might rule out finding an association with PROP tasting, which seems to be the case in some studies (32). Recently, however, Pickering and coworkers (33) demonstrated that PROP MTs and STs gave higher ratings than NTs of the sourness, bitterness, and astringency of red wines. It is

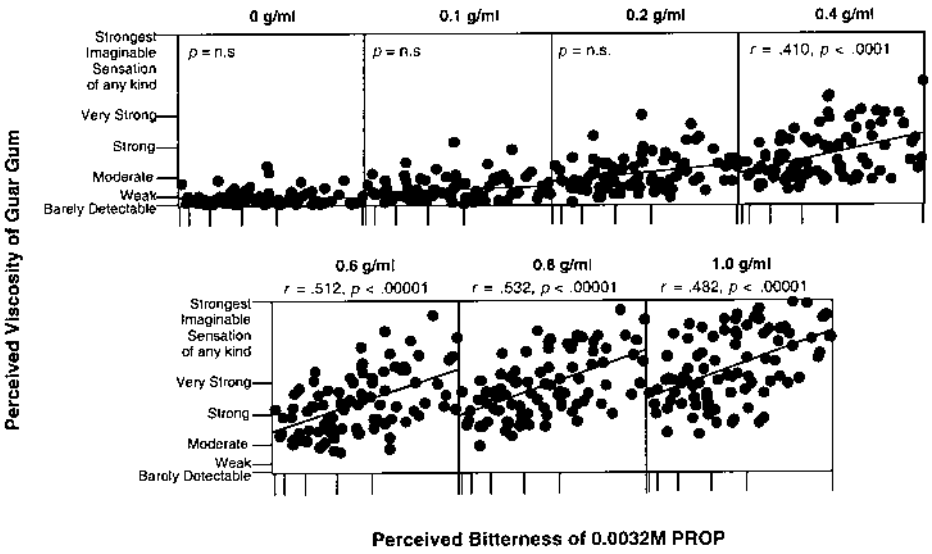

Figure 3 Relationship between ratings of the bitterness of 0.0032M PROP and the viscosity of guar gum across increasing concentrations (0–1.0 g/ml). PROP, 6-*n*-propylthiouracil.

certainly plausible that underlying PROP taste group differences in astringency is the activation of mechanoreceptors in the anterior tongue through the activity of the tongue in sensing the astringent sensations in other parts of the oral cavity. Such active sensing appears to be necessary in order to be able to perceive astringency (31).

The mechanism behind associations between tactile sensations and PROP sensitivity is suggested by research on two-point gap thresholds (26). A forced-choice threshold procedure in which subjects decided which of two stimulus pairs applied to the anterior tongue was a single point or two points was used. By using specially designed stimulators in which the distance between the two points could be varied from 0.25 mm to 8 mm, it was shown that the distance where two points rather than one were detected (gap threshold) was, for STs, half that of NTs (0.6 mm vs. 1.2 mm). In addition, gap threshold was significantly correlated with number of fungiform papillae ($r = 0.289$). This suggests that gap threshold may reflect interpapillae distance, and thus that fungiform papillae may be acting as individual tactile sensors. In STs, these tactile sensors are closer together than in NTs (and perhaps MTs), and thus STs should be capable of finer tactile discrimination.

Further evidence of differences in the tactile sensitivity of different PROP taster groups was found in a study that assessed the ability of subjects to identify, using the tongue, raised letters imprinted on blocks (Teflon) (34). Groups of STs, MTs, and NTs, defined by using LMS ratings of PROP, undertook a recognition threshold procedure for these letters. The height of the raised letters was manipulated in seven steps from 2.5 mm to 8 mm, with greater height easier to identify. The STs were able to identify letters correctly at a significantly lower letter height than were NTs. These data add further support to the notion that PROP taster groups vary in their sensitivity to oral tactile sensations presumably mediated by mechanoreceptors associated with fungiform papillae. Somewhat at odds with these studies are the data of Yackinous and Guinard (35), who found that although the area of the tongue where subjects were most sensitive to detecting stimulation with fine hairs (Von Frey filaments) was in the region most populated by fungiform papillae (dorsal, anterior tongue), there were no differences between taster groups in sensitivity in this region. On the median tongue, however, STs were most sensitive.

Individual differences in interpapilla distance may be the mechanism that underlies findings of associations between sensitivity to PROP and creaminess in foods (22,36) (see also Chapters 1 and 10 in this volume). A number of different sensory properties contribute to creaminess percep-

tion, including odor and mouthfeel characteristics such as viscosity and fat content. However, tactile sensations produced by the relative density of fat globules contribute to creaminess perception independently of viscosity (37). Prescott and colleagues (38) conducted a study that investigated whether differential sensitivity to variations in the tactile sensations produced by differences in fat content was the basis for differences in creaminess perception by different PROP taster groups. In two experiments, groups of NTs, MTs, and STs were asked to discriminate milks containing 0.4% fat from other samples containing either 1.15%, 1.9%, 2.65%, or 3.4% fat. Across these samples, fat globule density significantly increased, while viscosity remained approximately constant. The subjects were asked repeatedly to compare the reference sample (0.4% fat) with each of the other fat levels and indicate whether they were the same or

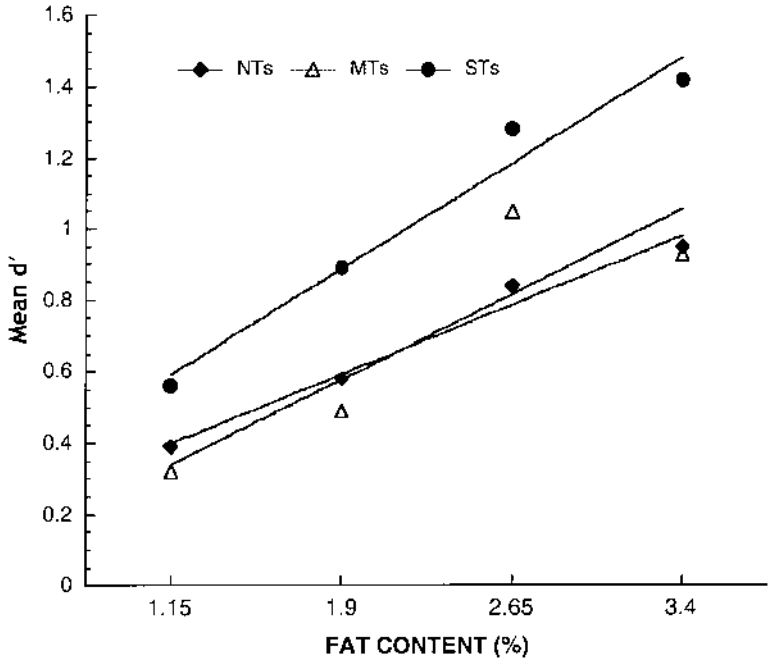

Figure 4 Mean d' values for the comparison of a reference sample of milk (0.4% fat) with milks of increasing fat levels (1.15%, 1.9%, 2.65%, 3.4%) for PROP NTs, MTs, and STs. PROP, 6-*n*-propylthiouracil; NT, nontaster; MT, medium taster; ST, supertaster.

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different. The measure of sensitivity used (*d'*) reflects the percentage of correct identifications of the higher fat level, taking into account false positive results. Values of *d'* increased with increases in the difference in fat content. Across all fat levels in both experiments, STs showed higher mean *d'* values than did MTs and NTs, representing better discrimination. The data from the second of these experiments are shown in Fig. 4. Better discrimination in this task points to an increased ability of STs to detect lower density distributions of fat globules, again implicating mechanoreceptors within fungiform papillae as arrays of individual sensors for tactile stimulation.

VI. THE TACTILE COMPONENT OF TASTES

There is increasing evidence from convergent sources that perception of tastes may involve considerable input from somatosensory fibers, in particular those sensitive to temperature and touch. A number of supposedly prototypical examples of basic tastes such as NaCl (salty) and citric acid (sour) have been shown to produce irritation at moderate to high intensities (39). Karrer and Bartoshuk (40) reported that subjects were able to provide ratings of tactile as well as taste qualities from quinine HCl, PROP, and citric acid. These apparently trigeminally mediated sensations also possess some of the psychophysical properties of established "pure" irritants such as capsaicin. For example, the irritation of NaCl sensitizes (increases in magnitude) with repeat stimulation, similarly to that of capsaicin burn (41). Particularly at high concentrations, the irritant/tactile (and quite possibly taste) properties of citric acid (39,40), NaCl (39), PROP, and quinine HCl (40) are also reduced after capsaicin desensitization. Reduction of taste intensities may imply cross-desensitization of tactile components of the taste qualities.

Other lines of evidence, primarily from animal studies, implicate somatosensory input as a partial determinant of the palatability of tastes (42). Again, this appears to be particularly the case at higher tastant concentrations, at the point where some tastants such as NaCl become aversive (43,44).

Various categories of somatosensory stimuli are also capable of inducing taste sensations. Cardello (45) noted that around 25% of fungiform papillae responded to tactile stimulation by fine wires with a taste quality, in particular sourness. More recently, tastes have been shown to be elicited by heated and cooled probes placed on areas innervated by cranial

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nerve VII and IX fibers (46), and by the application of the prototypical "pure" irritant, capsaicin, to circumvallate papillae (47). Further evidence points to tactile stimulation as crucial to perceptions of taste localization (48–51). In light of these data, Green (51) has queried whether it is appropriate to consider oral somatosensory sensations and tastes as providing distinct sensory information, except in the strict anatomical sense.

What these data imply is that it may be unclear, when assessing PROP taster group differences as a function of taste or somatosensory stimuli, which systems are responding differentially—or indeed it may be a moot point. Certainly, although reports of taste differences between PROP taster groups are relatively common, the magnitude of these differences is generally much lower that those reported for unequivocally somatosensory stimuli such as capsaicin irritation. This is not surprising given the relative degree of innervation of fungiform papillae by taste and somatosensory fibers. Moreover, the magnitude of taste differences appears to be related to stimulus concentration, even when all stimuli are well above threshold (see, for example, Ref. 9). Hence, taste differences between PROP taster groups may in fact partly reflect the effects of stimulation of somatosensory fibers, particularly as tastant concentrations increase. The use of insufficiently intense stimuli may partly explain (along with measurement issues; see Chapters 1 and 4 in this volume) why some researchers have not found significant associations between PROP tasting and ratings of other tastes.

VII. IMPLICATIONS FOR PERCEPTION OF SENSORY QUALITIES IN PRODUCTS

What these data also imply is that taster group differences in the perception of, and perhaps preference for, the sensory properties of foods and beverages may be most apparent where there is significant somatosensory stimulation. To date, however, this issue has received little attention. Given the repeated findings of PROP taster group differences in response to capsaicin in solution, we might expect similar differences for foods that produce obvious oral irritation—for example, spicy foods containing chili. However, many more foods may evoke somatosensory responses through significant degrees of carbonation, sourness, saltiness, or tactile stimulation (17). Hence, it also might be expected that PROP taster group differences are also apparent for foods with strong tastes. This appears to be evident in some of the studies comparing preferences of different

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taster groups. In addition to PROP/PTC tasters' having lower preferences for bitter foods (52–55), differences between tasters and NTs have also been found for foods that are sour, such as lemon juices, vinegar, and sauerkraut (53), or "sharp," for example, cheese (56).

Given differences in ratings of ethanol between PROP taster groups, it is also not surprising that taster status has also been linked to hedonic responses to ethanol, and as a consequence to differences in consumption frequency of alcoholic beverages (29). This may be determined by the responses to the bitterness or sourness of alcohol (33), as well as its irritant properties. However, it might be expected that if irritation is a more salient sensory quality than bitterness for STs, this group should be especially underrepresented as drinkers of high alcohol-content products. The proportion of cigarette smokers has been reported to be lower among PTC tasters than among NTs (57). Although this difference was explained in terms of bitter taste, irritation by nicotine may be an even more salient sensory aspect of smoke inhalation (58).

The role that fungiform papillae density may play in the perception of creaminess has been mentioned. The perception of graininess or grittiness in foods similarly depends on the consumer's ability to distinguish small particles and hence may be related to PROP taster status. Kirkmeyer and Tepper (see Chapter 6 in this volume), for example, have found that in describing dairy products, a group of STs were more likely than the NTs to use words such as *grainy* or *gritty*, presumably reflecting increased sensitivity to such qualities. Variations in the perception of oral somatosensory qualities are also likely to be important in determining the acceptability of oral care products, many of which contain irritants such as menthol. As perhaps the first demonstration of this, Rankin and colleagues (see Chapter 3 in this volume) have demonstrated the presence of ST and NT differences in the ratings of the irritant properties of a toothpaste, in the absence of differences in ratings of its taste qualities.

VIII. CONCLUSIONS

Clearly, the ability of PROP taster status to predict responses (both perceptual and hedonic) to oral somatosensory stimuli is worthy of further attention. Also an important area for further investigation is the relative extent to which differences in responses to tastes across PROP taster groups reflect either the gustatory or the somatosensory system. Given the interesting data emerging on the role of somatosensory input into the

taste experience, use of PROP taster groups, with their underlying differences in somatosensory innervation, may also become a valuable tool in investigating tactile and taste interactions and integration.

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5

Relationship of 6-*n*-Propylthiouracil Status to Bitterness Sensitivity

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I. INTRODUCTION

Since the early work of Weber, psychophysical studies have analyzed mean stimuli responses of subjects, with little attention paid to differences among individuals (1). More recently, factors influencing differences in individual responses have been investigated, with particular emphasis on responses to phenylthiocarbamide (PTC) and 6-*n*-propylthiouracil (PROP). This variability was first described by Fox (2) when his colleagues found PTC very bitter, but he was unable to taste it. Recent studies have found a broad continuum of threshold distributions within tasters and "nontasters." Bartoshuk and associates (3) proposed that three, rather than two, phenotypical groups exist: nontasters (NTs) who have two recessive genes; medium tasters (MTs) who have one recessive and one dominant gene; and supertasters (STs) who have two dominant genes (3).

Physiological differences between tasters and nontasters have been observed. The PROP supertasters have a higher density of fungiform papillae and a higher number of taste pores per taste papilla than PROP tasters, who in turn have higher values than those of PROP nontasters (4).

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More recently, women were reported to have a higher percentage of STs than men (5), a difference that may explain the lower PROP threshold reported for women than for men (6).

Despite these physiological differences, the relationship of PROP/PTC sensitivity to perception of other bitter compounds is not clear. Even the few studies relating sensitivity to PROP or PTC to thresholds of bitter compounds are inconsistent in their findings. Neither urea nor quinine thresholds were correlated with PTC thresholds; although the threshold of caffeine was significantly correlated with that of PTC, thresholds for urea and quinine were not (7). In contrast, Yokomukai and colleagues (8) found no relationship between PTC taster status and thresholds for caffeine and magnesium sulfate. Sucrose octaacetate (SOA) thresholds did not vary significantly as a function of either PTC (8) or PROP status (9).

The inconsistency in previous reports (8,10,11) may have resulted from variation in protocol for determining thresholds and in the method of defining PROP status. In earlier studies, such as that of Lawless (12), a single solution of PROP was used to discriminate nontasters from tasters. In contrast, Bartoshuk (13) and Drewnowski and associates (14) used ratios between ratings of PROP to NaCl solutions to discriminate between medium tasters and supertasters, and subjects (Ss) with PROP threshold above 2.0×10^{-4}M were identified as nontasters. In 2001 Tepper and colleagues (15) proposed classifying Ss by the relative intensity ratings of PROP and NaCl: NT, NaCl $>$ PROP, MT, NaCl = Prop; and ST, NaCl $\ll$ PROP. Another important factor explaining discrepancies in results is heterogeneity of taste populations; the age, race, and sex of the experimental Ss can have a large influence on results (5), especially in studies using a small number of Ss.

However, bitterness is perceived by several different transduction mechanisms, which also may contribute to variation in perception among individuals. Sucrose octaacetate increases Ca^{2+} concentration via a G-protein cascade involving phospolipase C (PLC) and 1,4,5-triphosphate (IP_3), whereas denatonium benzoate generates IP_3 and stimulates transducin, resulting in activation of phosphodiesterase (PDE) and decrease in cyclic adenosine monophosphate (cAMP) and increase in Ca^{2+} (16–18). These pathways may be complementary instead of exclusive, or they may use different receptors. In addition, SOA and denatonium block K^+ channels, as does quinine (19). Peri and associates (20) reported that quinine permeates taste cells and is a potent direct activator of transducin, which leads to the reduction of cAMP. Caffeine is thought to involve a direct activation of Ca^{2+} channels (21). Naringin induces production of IP_3 but does not affect cAMP levels, whereas limonin has been reported to

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decrease cAMP and increase IP_3 level (22). The transduction mechanism for PROP has not been studied, although a mouse taste receptor (T2R) that responds to PROP and denatonium has been reported human (23).

In this investigation, the relationship between subjects' sensitivity to selected bitter compounds and PROP status was explored. Second, to test the hypothesis that variation in sensitivity among individual results may relate to variation in transduction mechanisms, six bitter compounds with several different transduction mechanisms were selected for comparison with PROP.

II. MATERIAL AND METHODS

A. Stimuli

Seven bitter compounds were assessed: propylthiouracil (PROP) (Aldrich, Milwaukee, WI), limonin, naringin, sucrose octaacetate (SOA), denatonium benzoate (Sigma, St. Louis, MO), quinine sulfate (Fischer, NJ), and caffeine (Mallinckrodt, Paris, KY). The concentrations used for each compound varied in quarter-log steps. All solutions were prepared in deionized distilled water.

B. Protocol

Forty-one subjects participated in the experiment (23 females and 18 males, aged 22 to 50 yr). Subjects were presented with pairs of coded samples containing the test bitterant or water and asked to select which had the bitter taste. The determination of the thresholds was made by using a transformed, up-and-down method (TUDM) (22). Wrong answers led to the presentation of a more concentrated PROP solution, again paired with deionized water, whereas correct answers led to a second presentation of the same solution pair. If the answer was correct again, a lower concentration was presented. After discarding the first reversal point (between correct and incorrect answers), to prevent the effect of the starting concentration, the PROP threshold was calculated as the arithmetic mean of seven reversal points or the reversal points accumulated in 20 trials, whichever occurred first. Subjects rinsed thoroughly with deionized water after each pair of stimuli.

The PROP status of subjects was initially defined by using the PROP threshold values suggested by Bartoshuk (13,25). If thresholds were below 100μM, subjects were classified as tasters; if thresholds were above 200μM, they were categorized as nontasters (Fig. 1). The maximum intensity of

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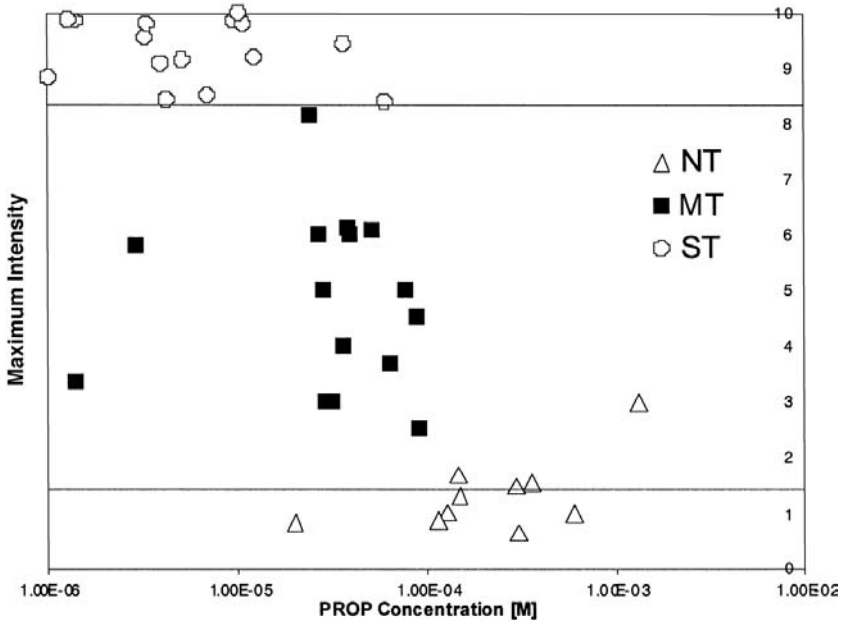

Figure 1 Classification of 41 subjects by 6-*n*-propylthiouracil status. PROP threshold [M] vs. maximum intensity of bitterness rated by time-intensity evaluation of 200mμM PROP. PROP, 6-*n*-propylthiouracil; NT, nontaster; MT, medium taster; ST, supertaster.

200μM PROP was rated in duplicate on a 10-cm unstructured line scale anchored at the ends by low and high, respectively, using time intensity (T-I) methodology. The mean maximum intensity for each S was used to make the final assignment of ST and MT status analogous to the protocol used by Tepper and coworkers (14). The STs were defined as those who rated intensity of PROP greater than 8.4 and NTs as less than 1.5, yielding 16 ST, 15 MT, and 10 NT (Fig. 1). Although 200μM PROP is below the threshold of several of the NTs, their low ratings of intensity (1 to 2 on the 10-unit scale) reflect the response to water that is frequently observed in T-I as Ss start to move the mouse as the sample is ingested.

C. Data Analysis

Analyses of variance were conducted with Ss nested by PROP status, gender, or cluster. Pearson product moment correlations were calculated

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on threshold values between compounds. Cluster analysis was done by using Ward's method for Euclidean distances. All calculations were carried out by using SAS for Windows Version 6.1 (SAS, Cary, NC).

III. RESULTS

The distribution frequencies of thresholds for the seven compounds are shown in Fig. 2. Although the separation of individuals into the three classes of PROP tasters was not straightforward, the mean PROP thresholds of the PROP status classes were highly significantly different ($F(2, 38) = 11.06$): ST, 12.7μM; MT, 42.6μM; NT, 345μM. Despite the considerable

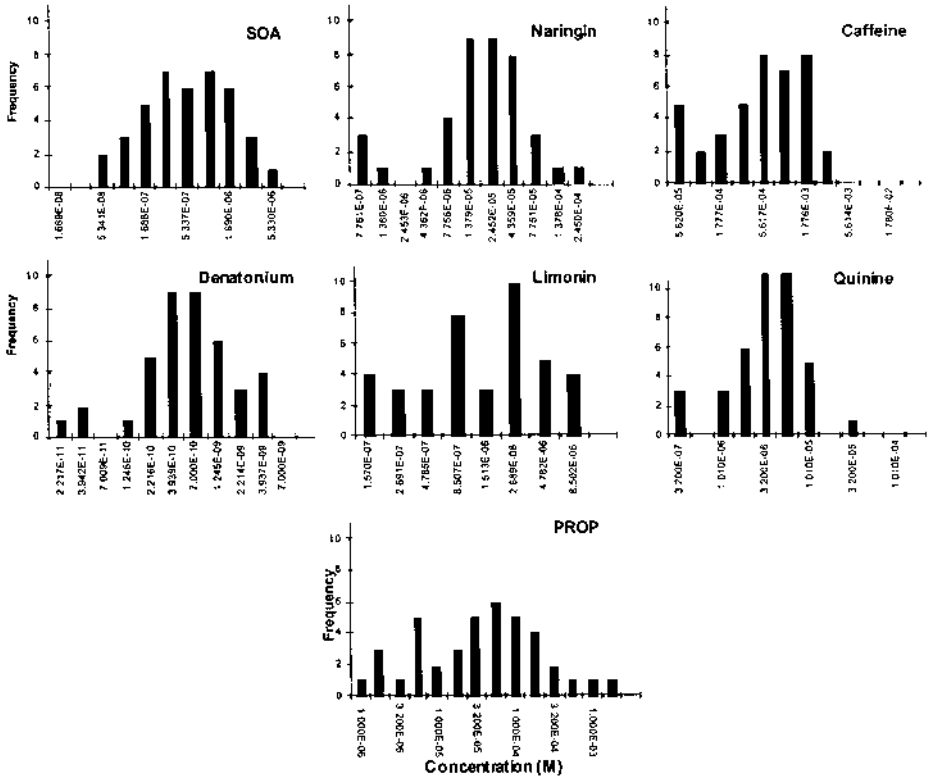

Figure 2 Frequency distribution of thresholds of 41 subjects. SOA, sucrose octaacetate; PROP, 6-*n*-propylthiouracil.

variation in thresholds for the six bitter tastants within each PROP class, PROP nontasters had statistically significantly higher thresholds than supertasters for SOA, caffeine, naringin, and PROP [$F(2, 38) = 3.00$ to 5.48, $p < 0.06$ to 0.001] (Table 1). However, no difference in thresholds among PROP classes were found for denatonium, limonin, and quinine [$F(2, 38) = 0.72$ to 1.34].

Reexamination of these data by gender revealed that PROP thresholds differed significantly across PROP classes for both genders: men, $p < 0.006$; women, $p < 0.002$. In contrast, SOA, naringin, and caffeine thresholds differed significantly as a function of PROP status only for females [$F(2, 20) = 2.73$ to 7.32, $p < 0.089$ to 0.004] (Table 2).

In contrast to previous studies in which women have been reported to have lower PTC thresholds ($n = 214$) (26) or lower PROP thresholds ($n = 985$) (5) than men, in the present study, women had an insignificantly higher threshold for PROP (143.8μM vs. 54.5 μM). Between genders, threshold values were significantly different for one compound: caffeine was higher for women (0.73mM) than for men (0.44mM), [$F(1, 39) = 3.73$, $p < 0.06$].

As shown in Table 3, PROP thresholds were significantly correlated with the thresholds of caffeine, naringin, and SOA across all Ss and for women. In contrast, for men there were no significant correlations with PROP. Over the 41 Ss, significant correlations were seen between the other compounds (Table 3). The SOA was correlated with naringin, denatonium, and limonin; naringin, with limonin and quinine; denatonium, with quinine and caffeine. However, when these correlations between com-

Table 1 Mean Thresholds[a] [M] for Supertasters, Medium Tasters, and Nontasters and Level of Significance (p)

	ST (7 F 9 M)		MT (9 F 6 M)		NT (6 F 4 M)		p
PROP	1.27E-05	a	4.26E-05	a	3.45E-04	b	0.001
Caffeine	4.00E-04	a	6.23E-04	ab	9.32E-04	b	0.049
Naringin	1.26E-05	a	1.98E-05	a	4.52E-05	b	0.008
SOA	5.11E-07	a	5.67E-07	a	1.35E-06	b	0.062
Denatonium	4.71E-10		9.41E-10		7.82E-10		0.274
Limonin	1.75E-06		1.72E-06		2.60E-06		0.493
Quinine	2.79E-06		4.39E-06		2.91E-06		0.389

[a] Different letters within a row denote significant differences ($p < 0.05$). ST, supertaster; MT, medium taster; NT, nontaster; PROP, 6-*n*-propylthiouracil; SOA, sucrose octaacetate.

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Table 2 Mean Thresholds[a] [M] by Gender and 6-*n*-Propylthiouracil Status for Compounds Varying Significantly Across 6-*n*-Propylthiouracil Status ($p < 0.10$)

Males ($n = 18$)				
Compounds	ST ($n = 9$)	MT ($n = 5$)	NT ($n = 4$)	p
PROP	1.51E-05 a	5.42E-05 a	1.43E-04 b	0.006
Females ($n = 23$)				
	ST ($n = 7$)	MT ($n = 10$)	NT ($n = 6$)	p
PROP	5.77E-06 a	3.67E-05 a	4.79E-04 b	0.002
Caffeine	4.01E-04 a	7.53E-04 ab	1.22E-03 b	0.089
Naringin	1.16E-05 a	2.02E-05 a	6.63E-05 b	0.004
SOA	4.73E-07 a	5.55E-07 a	1.83E-06 b	0.059

[a] Different letters within a row denote significant differences; *p,* level of significance. MT, medium taster; ST, supertaster; NT, nontaster; PROP, 6-*n*-propylthiouracil; SOA, sucrose octaacetate.

pounds are inspected separately for each gender, the pattern of correlations for men is different from that observed for women, which is similar to the data for all 41 Ss (Table 3).

A cluster analysis of the threshold values (for all compounds but PROP) revealed five clusters, of which one contained only one S (female NT PROP threshold = 0.00132M), which suggests a correspondence with PROP sensitivity. The subjects with the lowest thresholds for all compounds were found in cluster 1 ($n = 13$; ST = 6, MT = 6, NT = 5; six females); cluster 4 ($n = 4$; MT = 2, NT = 2; four females) contained the least sensitive subjects. With the exception of quinine and limonin, which did not differ among clusters, cluster 4 had significantly higher mean thresholds for all compounds than the other clusters (Table 4).

IV. DISCUSSION

The frequency distribution for PROP thresholds of these 41 Ss (Fig. 2) was not bimodal, as reported previously for PTC (1,7) and PROP (13,24, 27,28). However, the thresholds for caffeine, SOA, and naringin differed significantly as a function of PROP status, in contrast to the results of Boughter (9), who found no effect of PROP status on SOA thresholds.

Table 3 Correlation Coefficients Between Compounds for Males and Females[a]

A. For all subjects ($df = 39$) ($n = 41$)

	PROP	SOA	Naringin	Limonin	Quinine	Caffeine
PROP	1.00					
SOA	0.75***	1.00				
Naringin	0.50***	0.62***	1.00			
Limonin	0.15	0.09	0.18	1.00		
Quinine	−0.11	0.08	0.23	0.34*	1.00	
Caffeine	0.43**	0.41**	0.50***	0.25	0.07	1.00
Denatonium	−0.06	0.11	0.12	0.16	0.59***	0.48**

B. For males ($df = 16$) ($n = 18$)

	PROP	SOA	Naringin	Limonin	Quinine	Caffeine
PROP	1.00					
SOA	0.21	1.00				
Naringin	0.25	0.32	1.00			
Limonin	0.00	0.26	0.70**	1.00		
Quinine	−0.02	0.29	0.61*	0.45#	1.00	
Caffeine	0.18	0.20	0.39	0.59*	−0.04	1.00
Denatonium	-0.11	0.32	0.16	0.31	0.72***	0.2

C. For females ($df = 21$) ($n = 23$)

	PROP	SOA	Naringin	Limonin	Quinine	Caffeine
PROP	1.00					
SOA	0.80***	1.00				
Naringin	0.49*	0.64***	1.00			
Limonin	0.14	0.03	0.03	1.00		
Quinine	−0.23	−0.01	0.14	0.29	1.00	
Caffeine	0.42*	0.43*	0.48*	0.11	0.16	1.00
Denatonium	−0.05	0.05	0.15	0.08	0.43*	0.69***

[a] PROP, 6-*n*-propylthiouracil; SOA, sucrose octaacetate; #, *, **, and *** denote, respectively, $p = 0.06$, $p < 0.05$, $p < 0.01$, and $p < 0.001$.

There were significant correlations between PROP thresholds and those of naringin, caffeine, and SOA for all Ss and for females, but not for men. Consistently with the present study, significant correlations have been found between PTC and caffeine (7), but not between PTC and quinine (1,7).

Although higher thresholds do not necessarily imply lower responses to suprathreshold concentrations (29), the effect of PROP status on bitterness intensity ratings of suprathreshold levels of other stimuli has

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Table 4 Mean Thresholds[a] [M] and 6-*n*-Propylthiouracil Status Composition for Four Clusters

	Cluster number							
	1		2		3		4	
Compounds	Means							
PROP	2.19E-05	a	6.24E-05	a	1.19E-04	ab	2.27E-04	bc
Caffeine	1.13E-04	a	4.94E-04	b	1.10E-03	c	1.80E-03	d
Naringin	1.37E-05	a	1.77E-05	a	2.00E-05	a	6.57E-05	b
SOA	3.81E-07	a	5.40E-07	a	7.63E-07	a	1.53E-06	b
Denatonium	3.00E-10	a	7.23E-10	a	9.82E-10	ab	1.79E-09	b
Quinine	3.16E-06	a	3.29E-06	a	3.94E-06	a	4.48E-06	a
Limonin	1.09E-06	a	2.09E-06	a	3.29E-06	a	2.48E-06	a
Status	Cluster composition							
ST	8		6		2		0	
MT	5		6		2		2	
NT	0		5		2		2	
Sex								
Male	7		10		3		0	
Female	6		7		3		4	

[a] Within a row, means with different letters differ significantly ($p < 0.05$). PROP, 6-*n*-propylthiouracil; SOA, sucrose octaacetate; ST, supertaster; MT, medium taster; NT, nontaster.

been extensively examined. In the present study, PROP STs had lower thresholds for caffeine than NTs, consistently with Bartoshuk's finding that PROP tasters rated bitterness of caffeine higher than nontasters (13). However, other suprathreshold studies reported no variation in ratings of caffeine (30,31). No variation in quinine thresholds across PROP status was found in the present study, consistently with other studies, in which no difference in quinine ratings was found as a function of PROP status (31) or number of papillae (32). In contrast, quinine was rated more bitter by tasters than by nontasters (30,33).

Pangborn (1) suggested in 1981 that averaging over subjects can conceal important information in scaling, as well as in threshold measurement. This point is especially important in studies of bitterness, in which subjects vary widely in sensitivity, as illustrated in the present study for seven compounds. Several studies have reported females to be more sensitive than males (5,26,34); in contrast, in the present study men had a significantly lower threshold for one compound (caffeine). This suggests

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that much of the variation across studies may arise in part from the different composition of populations with respect to gender.

As shown by the variation in sensitivity between genders and among PROP classes, the relationship between PROP sensitivity and that to other bitter compounds is influenced by both factors. Therefore, large populations balanced by gender and PROP status should be studied to increase the validity of conclusions.

Although widely differing patterns of sensitivity to these bitter compounds were seen, the limited information about the taste transduction mechanisms of these compounds failed to suggest a real basis for the clustering of compounds or clustering of subjects by thresholds. Moreover, studying patterns of Ss sensitivities oversimplifies the issue. Results from nerve recordings and studies of taste cell responses suggest that the bitter sensation occurs through activation of multiple heterogeneous taste cells (35) and multiple transduction pathways (20).

V. CONCLUSION

6-*n*-Propylthiouracil taster status does not predict sensitivity to other bitter compounds. Although PROP status is correlated with sensitivity to caffeine, naringin, and SOA, this correlation is only observed for females. No difference in sensitivity to denatonium, limonin, or quinine as a function of PROP status was found for either gender. Correlations of thresholds between compounds are different for men and women, suggesting that the role of gender needs to be explored further in understanding mechanisms of perception of bitterness.

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6

A Current Perspective on Creaminess Perception and 6-*n*-Propylthiouracil Taster Status

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I. INTRODUCTION

Creaminess is a major sensory attribute of dairy products and a primary driver of consumer acceptance. Although the perception of dairy products can be modified by varying fat content, flavor, appearance, or texture (1–5), it is not always clear how these changes alter *creaminess*. Moreover, the term creaminess is redundant since consumers use it to describe both the flavor and the texture of dairy products (6,7). Obtaining a more fundamental understanding of the perceptual cues and attributes for creaminess perception could lead to greater insight into the underlying dimensions of creaminess. Studying individual differences in perception through 6-*n*-propylthiouracil (PROP) classification of subjects might provide insight into this issue.

Response to the bitter taste of PROP is genetically determined (8,9). In the North American Caucasian population, approximately 30% are insensitive to the bitterness of PROP and are classified as nontasters (10).

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The remaining 70% detect the bitterness of PROP and are classified as tasters (10). A subset of tasters (~25%) perceive PROP as extremely bitter and are considered supertasters (11). Thus, taste sensitivity to PROP follows a trimodal distribution with nontaster, medium-taster, and supertaster classifications.

Although not all studies agree (12,13), PROP tasters are typically more sensitive than nontasters to a range of sensory attributes, including bitterness, sweetness, oral irritation, and fat (14–21). Among these, fat content and sweetness are of particular relevance to the perception of creaminess in dairy products. However, studies looking at fat- and sucrose-modified dairy products have not produced the expected differences in perception between PROP nontaster and taster groups (22,23). Thus, the role of PROP status in the perception of creaminess remains controversial.

A number of factors, such as issues in study design, sample preparation, classification of panelists, and scaling, might contribute to these conflicting findings (22–24). Almost all studies used laboratory samples that may not approximate real dairy foods. Data are lacking in actual products. It is also unclear how manipulations of sweetness affect the perception of fat in a complex system. Another issue relates to visual cues, which can dominate the evaluation of fat-containing foods, confounding sensory judgments. Finally, issues of classification of panelists and scaling also might influence research outcomes; they are addressed in Chapters 1, 3, and 4 in this volume. This chapter evaluates current findings in the literature in light of these issues and presents new experimental data to address these conflicts.

II. 6-*n*-PROPYLTHIOURACIL AND FAT PERCEPTION

6-*n*-Propylthiouracil tasters are more sensitive to the textural sensations of fat. This effect was first demonstrated by Tepper and Nurse in a study of salad dressings (20). Medium tasters and supertasters were able to discriminate between 10% and 40% fat salad dressings, whereas nontasters assessed the fat content of the samples as equivalent.

This study (20), as well as others, has shown that supertasters have greater papillae density on the tip of the tongue than do nontasters (11, 20, 21). Papillae density is associated with trigeminal nerve innervation in rodents (25), and it is assumed that this configuration is also correlated with oral mouthfeel sensations in humans (26). This physical advantage

might explain why PROP tasters have greater acuity for the texture of fats. A more detailed discussion of the contribution of oral sensation is provided in Chapter 4 in this volume.

III. 6-*n*-PROPYLTHIOURACIL AND CREAMINESS

Duffy and coworkers (27) studied the perception of creaminess intensity among taster groups for dairy products ranging in fat content from 0.5% to 54%. The PROP supertasters gave the highest ratings of creaminess to samples with greater than 11% fat. Prescott and colleagues (28) also showed that supertasters discriminated between the creaminess of 2.65% and 3.4% fat in milk versus the 0.4% fat reference sample to a greater degree than medium tasters or nontasters.

Drewnowski and coworkers (22) showed no difference in perception among PROP taster groups for dairy products varying in fat content (3.5%, 10.5%, and 30% fat) and sweetness (2%, 4%, 8%, 16%, and 32% sucrose wt/wt). Yackinous and Guinard (23) also showed no difference among PROP taster groups for creaminess perception of several fat-containing products, including vanilla puddings and chocolate milks varying in fat content and dairy flavor.

These negative findings may be due to the complex nature of the samples, as several variables, including fat content and sweetness or flavor, were simultaneously manipulated (22,23). Also, the evaluation of large sample sets in these studies might have fatigued subjects and minimized observed differences. Another possibility is that sweetness confounded the effects of fat in these studies. Sweetness is known to enhance creaminess perception (29,30). However, Drewnowski and Schwartz (31) showed that high sweetness concentrations depressed the perception of fat in dairy mixtures. It is possible that the presence of sweetness in dairy products creates "sensory confusion." Since PROP tasters are theoretically more sensitive to both fat and sweetness (17,20), they may be more susceptible to the masking effects of the sweetness. Previous study designs did not permit sweetness to be evaluated as an independent variable.

Also, the contribution of appearance characteristics cannot be overlooked. Visual cues strongly influence sensory judgments and may reduce or eliminate oral sensory differences due to PROP status. Tepper and Nurse (20) and Prescott and coworkers (28) minimized visual cues via sample preparation or utilization of red lights. Neither Drewnowski and

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colleagues (22) nor Yackinous and Guinard (23) controlled for possible visual differences between the samples.

IV. SWEETENED AND UNSWEETENED MODEL MILK SYSTEMS

The following study was conducted to untangle the relationship between sweetness and fat content in the perception of creaminess among PROP classified individuals. Subjects evaluated separate sets of sweetened and unsweetened milk model systems varying in fat (0%, 5% or 20%). It was hypothesized that medium tasters and supertasters would give higher ratings of creaminess than nontasters as the fat content of unsweetened milk samples increased. However, medium tasters and supertasters were not expected to give higher creaminess ratings to the sweetened samples across fat concentrations because of the masking effect of sweetness on the perception of creaminess for these groups.

The study was conducted with 76 adult consumers from Rutgers University who were regular milk drinkers (two or more times per month). A subject was classified as a PROP nontaster (NT), medium taster (MT), or supertaster (ST) by responses to the intensity of PROP- and sodium chloride-impregnated filter paper disks (32) on the labeled magnitude scale (33,34). The means $\pm$95% confidence intervals were calculated and used to establish numerical cutoff scores for taster group classification (32). The NTs typically had PROP intensity scores $\leq$15, STs rated PROP $\geq$67, and the intermediate group considered were MTs. Sodium chloride was used as a reference.

Unsweetened and sweetened (6% sucrose) milk mixtures were formulated by homogenizing fat-free milk with 0%, 5%, or 20% (w/v) vegetable oil. Samples were prepared to have similar visual appearance and were evaluated under red lights. Creaminess intensity and sweetness intensity were assessed by using a 15- point line scale (0 = none at all, 15 = extremely strong). Overall liking was assessed on a 9-point hedonic scale (1 = dislike extremely, 5 = neither like nor dislike, 9 = like extremely).

As expected, sweetened milk samples were rated as more sweet than unsweetened samples across all groups (see Fig. 1) [sweetness main effect $F(1, 150) = 172.61$, $p \leq 0.001$]. Creaminess ratings increased across all concentrations of fat for all subjects regardless of sweetness content (see Fig. 2) [fat content main effect $F(2, 298) = 72.94$, $p \leq 0.001$]. However,

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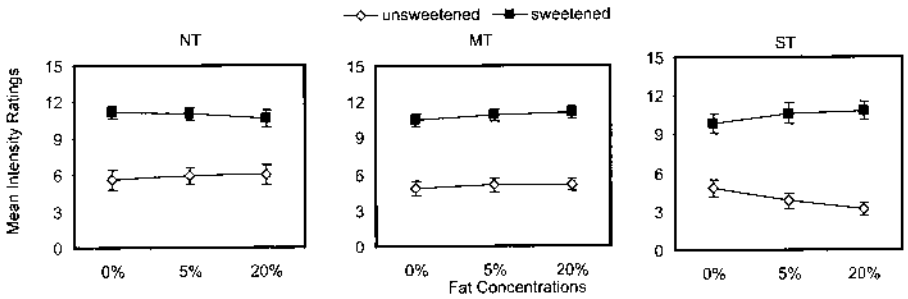

Figure 1 Sweetness intensity ratings for unsweetened and sweetened (6% sucrose) milk samples containing 1%, 5%, or 20% fat. Sweetened milk samples were rated as more sweet than unsweetened samples by nontasters, medium tasters, and supertasters of PROP [sweetness main effect $F(1, 150) = 172.61$, $p \leq 0.001$]. NT, nontaster; MT, medium taster; ST, supertaster; PROP, 6-*n*-propylthiouracil.

the creaminess ratings rose more rapidly across fat concentrations for PROP medium tasters and supertasters than for nontasters [taster group main effect $F(4, 298) = 3.33$, $p \leq 0.01$]. Thus, sweetness contributed by 6% sucrose did not alter creaminess perception for any group. Liking ratings showed a slight inverted U-shaped function across fat concentrations that were also unaffected by the addition of sweetness (see Fig. 3) [concentration main effect $F(2, 300) = 2.62$, $p \leq 0.07$]. However, liking

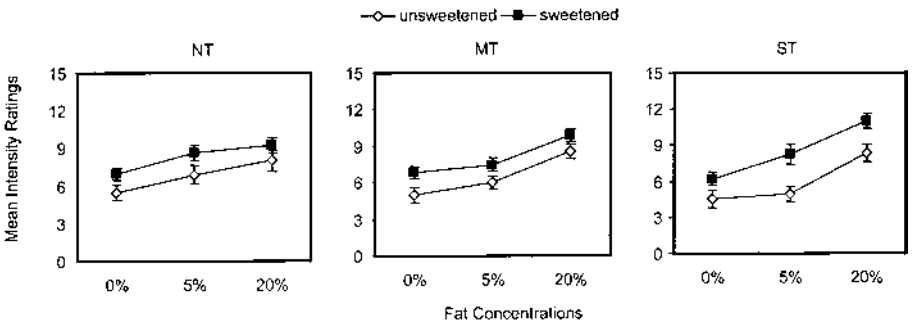

Figure 2 Creaminess intensity ratings rose more rapidly across fat concentrations (1%, 5%, and 20% fat) for PROP medium tasters and supertasters than for nontasters [taster group main effect $F(4, 298) = 3.33$, $p \leq 0.01$] regardless of sweetness content. NT, nontaster; MT, medium taster; ST, supertaster; PROP, 6-*n*-propylthiouracil.

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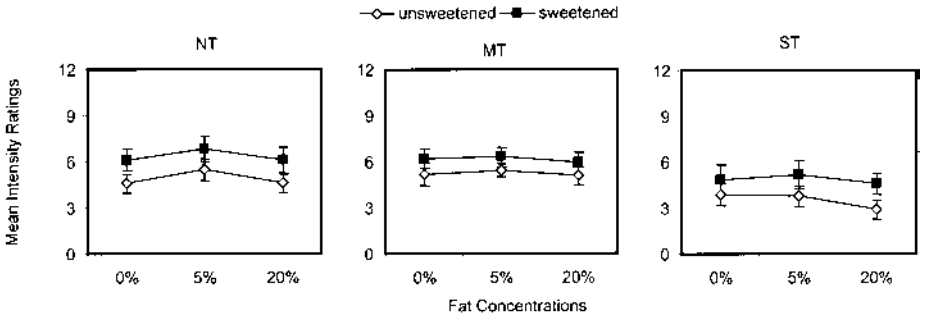

Figure 3 Liking varied inversely with PROP taster status [taster status main effect $F(2, 150) = 4.62$, $p \leq 0.01$]. Nontasters liked all of the samples most and supertasters liked all of the samples least. Liking was unaffected by the addition of sucrose [concentration main effect $F(2, 300) = 2.62$, $p \leq 0.07$]. NT, nontaster; MT, medium taster; ST, supertaster; PROP, 6-*n*-propylthiouracil.

ratings varied inversely with taster status such that nontasters liked all of the samples most and supertasters liked all of the samples least [taster status main effect $F(2, 150) = 4.62$, $p \leq 0.01$].

The results of the study showed a moderate effect of PROP taster status on the perception of creaminess intensity and liking of fluid dairy samples. Adding sucrose shifted the ratings upward for all subject, but did not alter the perception of creaminess as a function of taster status. Thus, the hypothesis of sweetness "masking" was not supported by these data. These findings are consistent with those previously reported by Duffy and coworkers (27) showing that creaminess ratings increased more rapidly across fat concentrations for supertasters than for medium tasters and nontasters.

PROP status was inversely associated with liking of the samples, but the effect was small. These findings are in the same direction as but less robust than those of Keller and colleagues (35), who found that nontaster children were more accepting of full-fat milk than taster children.

V. UNDERLYING DIMENSIONS OF CREAMINESS PERCEPTION

All previous research investigating PROP and creaminess examined only a small number of attributes and then analyzed each one separately. These

univariate analyses capture only a limited amount of information. To understand the underlying dimensions of creaminess perception better, multivariate techniques, such as free-choice profiling (FCP), can be employed; FCP differs from conventional descriptive analysis in that subjects are not trained on a specific lexicon or intensity ratings. Rather, subjects utilize their own words/descriptors to describe the products. Free-choice profiling has been used in a variety of studies (36–39), but none has included PROP classification.

In FCP, the individual evaluations are consolidated through Generalized Procrustes Analysis (GPA) and projected onto a common perceptual space (40); GPA is an iterative statistical process to condense the individual subjects' ratings of the foods together on the basis of numerical patterns in the data rather than their lexicon. This analysis also allows the products to be related to the perceptual dimensions. Real food products were investigated, as previous studies have been limited to the investigation of laboratory samples. The hypotheses tested in this study were that (a) PROP supertasters are more sensitive to fat and creaminess in real food products than nontasters and (b) higher perception of creaminess by supertasters relates specifically to the textural components of the samples.

Two pools of PROP-classified subjects were established for this research. The first pool consisted of 76 semi-trained International Flavors & Fragrances (IFF) employees. These subjects were experienced evaluators with technical background in the food industry and regularly participated in sensory evaluations. They had not been formally trained in descriptive analysis. The second pool consisted of 250 consumers. A subset of the consumer pool also participated in studies by Rankin and associates on PROP classification methodology described in Chapter 3 in this volume. Taster status was obtained by collecting subjects' responses to the intensity of 3.2 mmol/1 PROP and 0.1 mol/1 NaCl solutions (41) on the labeled magnitude scale (33,34). Groups of PROP nontasters, medium tasters, and supertasters were identified by using K-means cluster analysis for three groups and establishing numerical cutoffs and $\pm 95\%$ confidence intervals for PROP (41). In order to maximize group differences, subjects from the ends of the distribution (nontasters and supertasters) were selected to participate in subsequent research. A complete description of this study can be found in Kirkmeyer and Tepper (2003) (47).

The foods chosen for the study represent a range of market dairy products. An earlier study by Kokini and Cussler (42), examining the

texture perception in the mouth, used a similar set of samples. The nine dairy products were obtained from a local New Jersey grocery store and were chosen on the basis of their fat content, viscosity, sweetness, and flavor. The dairy products are shown in Table 1.

From the pool of semitrained subjects, 10 NTs and 10 STs were selected to participate in the FCP study. Subjects were matched on demographic variables to prevent confounding of the PROP group effects. Subjects were prompted to generate words to describe the salient appearance, taste/flavor, and mouthfeel/texture characteristics of the products. Then, subjects used these terms to evaluate, in duplicate, the set of nine dairy products by using a 15-cm line scale. Generalized Procrustes analysis (GPA) was used to condense the individual subjects' ratings into an *n*-dimensional space. To interpret the perceptual space, three pieces of information are assimilated: (a) the dimension loadings (how much each dimension captures the total variance), (b) the relation of the attributes to the dimensions, and (c) the product orientations in the space.

Perceptual spaces were generated by GPA separately for nontasters and supertasters. In developing the models of perception, the appearance characteristics were found to have a large contribution to the model, (contributing an additional 25% of variance to both models) but did not distinguish nontasters and supertasters. Previous studies with FCP have shown that including appearance terms in the modeling inordinately influenced the perceptual models (6). Thus, in the perceptual spaces shown here, the appearance terms were excluded to focus on the contributions of taste and texture to the perception of the products. The GPA models for nontasters and supertasters are illustrated in Figs. 4 and 5, respectively.

The models for both the nontasters and the supertasters captured approximately 54% of the variance in the data in two dimensions. For nontasters, the percentage of variance accounted for in Dimensions 1 and 2 was approximately equal (28% and 26%, respectively). For supertasters, Dimension 1 accounted for a higher percentage of variance in the model (34%) as compared to Dimension 2 (20%).

For nontasters, Dimension 1 was described as a continuum from sweet taste/flavor to sour and buttermilk taste/flavor. Dimension 2 was described by a dairy flavor/texture continuum including the terms milky and bland taste/flavor on one end, to mouthcoating, thick mouthfeel/texture on the other end. For supertasters, the two dimensions are rotated such that Dimension 1 reflected a gradation of dairy flavor and texture terms. The terms rich, buttery, creamy taste/flavor and creamy, thick,

Table 1 Sample Descriptions of Dairy Products Used in Free-Choice Profiling and Consumer Research Studies

Food	Abbreviated name	Fat content, %	Brand name
Vanilla yogurt	Van yog	1.5%	Dannon Vanilla Lowfat Yogurt Grade A 1% milk fat, Dannon Company, Inc., Tarrytown, NY
Sweetened condensed milk	Swt cond mlk	7.5%	Borden, Eagle Brand, Columbus, OH
Whole milk	Whole mlk	3.5%	Lehigh Valley Dairies, Lansdale, PA
Skim milk	Skim mlk	0%	Lehigh Valley Dairies, Lansdale, PA
Light cream	Lt cream	36%	Lehigh Valley Dairies, Lansdale, PA
Cream cheese	Cream cheese	35%	Philadelphia Original Cream Cheese, Kraft Foods, Glenview, IL
Vanilla ice cream	Van ice cream	13%	Breyer's Natural Vanilla Ice Cream, Good Humor-Breyer's Ice Cream, Green Bay, WI
Whipped light cream	Wpd cream	25%	Reddi Whip Original Ultra Pasteurized Sweetened Whipped Light Cream, Beatrice Foods, Indianapolis, IN
Sour cream	Sour cream	18%	Breakstone's Sour Cream Grade A Pasteurized Homogenized, Kraft Foods, Inc., Glenview, IL

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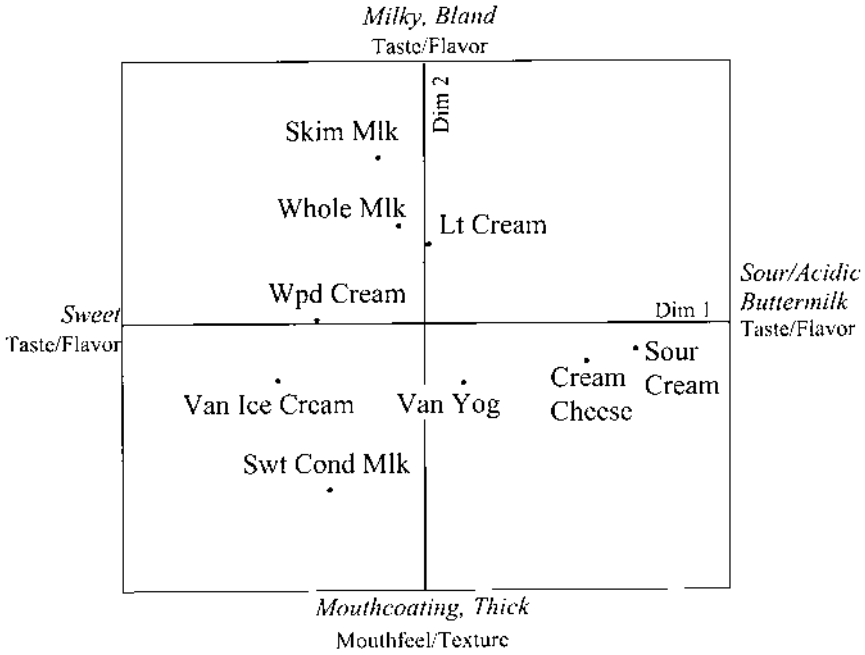

Figure 4 Generalized Procrustes analysis for nine dairy products by 10 nontasters: Dimension 1 horizontal axis (described as *Sweet* to *sour* basic taste continuum with 28.6% variance) versus Dimension 2 vertical axis (described as *Dairy* flavor/texture dimension with 26.3% variance) with total variance accounted for of 54.9%.

coating, heavy mouthfeel/texture described one end of the continuum. The other end of the continuum included watery, light mouthfeel/texture and bland, watery, milky/dairy taste/flavor. Dimension 2 consisted of basic tastes plus textural terms, such that sour and salty taste/flavor were contrasted with grainy, gritty, sandy mouthfeel/texture. The latter textural terms were absent from the nontasters' basic taste dimension.

However, the relative positions of the foods in the two-dimensional spaces were similar for nontasters and supertasters. The foods that loaded on the sweet–sour continuum (Dimension 1 for nontasters and Dimension 2 for supertasters) included sour cream, cream cheese, and vanilla ice cream. Sweetened condensed milk, whole milk, and skim milk loaded high on the dairy flavor/texture dimension (Dimension 2 for nontasters and

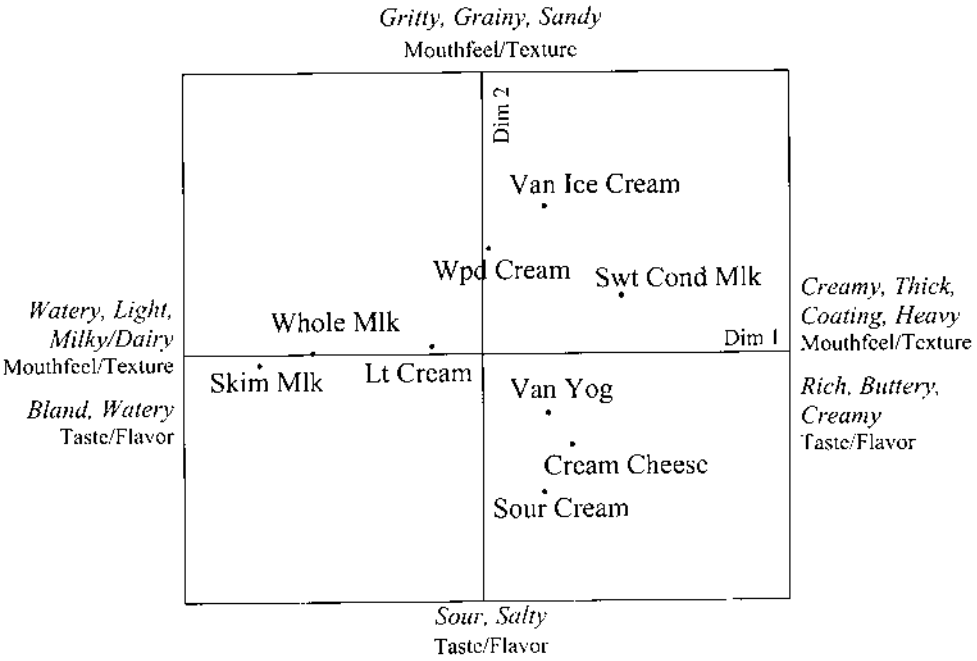

Figure 5 Generalized Procrustes analysis for nine dairy products by 10 supertasters: Dimension 1 horizontal axis (described as *Dairy* flavor/texture dimension with 34.3% variance) versus Dimension 2 vertical axis (described as *Sweet* to *sour* basic taste continuum 19.9% variance) with total variance accounted for of 54.2%.

Dimension 1 for supertasters). Thus, for supertasters and nontasters, the foods maintained the same position relative to the major axis; only the order of the dimensions was reversed.

These perceptual spaces can be interpreted in the following way: The models for both supertasters and nontasters included a dairy flavor/texture axis and a basic taste axis. However, supertasters weighted the dairy flavor/texture dimension more heavily than the basic taste dimension, whereas nontasters weighted the dimensions equally. Thus, the dairy flavor/texture dimension was more important for supertasters to explain their overall perception than for nontasters.

The manner in which nontasters and supertasters described the dimensions also differed. Supertasters used a more complex vocabulary with respect to the type and number of flavor and texture terms. For the

dairy flavor/texture dimension, nontasters included the terms milky, bland flavor, and thick, mouthcoating texture. Supertasters used these same terms but also included the terms buttery, rich, and creamy flavor. For the basic taste dimension, nontasters used the terms sweet and sour, and supertasters added particulates.

These data suggest that for supertasters, dairy flavor and texture contributed more heavily to overall perception of the products than for nontasters. Also, supertasters associated more textural terms than nontasters with their perception of the sample. These differences might be attributable to greater sensitivity to oral texture associated with taste bud density and trigeminal innervation of the tongue (11,20,21,26). Yet, despite the different cues that PROP supertasters and nontasters used to describe the products, the relative positions of the foods along the two dimensions were similar for nontasters and supertasters, suggesting that the overall perception of creaminess was similar for both groups.

VI. CREAMINESS AS A UNIVERSAL CONSTRUCT

A series of studies was conducted by Kokini and colleagues (42–44) to identify the primary descriptors of texture for liquid and semisolid foods and to relate assessment of these descriptors by human and instrumental measures. Regression analysis identified several terms, including *smoothness*, *thickness*, and *slipperiness*, that could be used to predict a larger group of attributes. Each attribute was closely related to a specific force in the mouth. Then, a predictive model for creaminess was developed from subjects' evaluations of two selected attributes, smoothness and thickness. A linear regression equation ($R^2 = 0.81$) ordered the products from low to high creaminess. The rank order of the samples from low to high creaminess was skim milk, whole milk, cream, cream topping, ice cream, to cream cheese (see Fig. 6).

In the free-choice profiling study, an ordering of products was also obtained along the dairy flavor/texture dimension. As the Kokini and Cussler study (42) provided a framework for sample selection for the FCP study, the products' orderings can be compared across studies. Results showed that the product arrangement along the dairy flavor/texture continuum for both nontasters and supertasters was strikingly similar to that obtained by Kokini and Cussler (42), except that cream cheese and ice cream were reversed in order. These results, obtained by using very different study designs, imply that the overall integration of

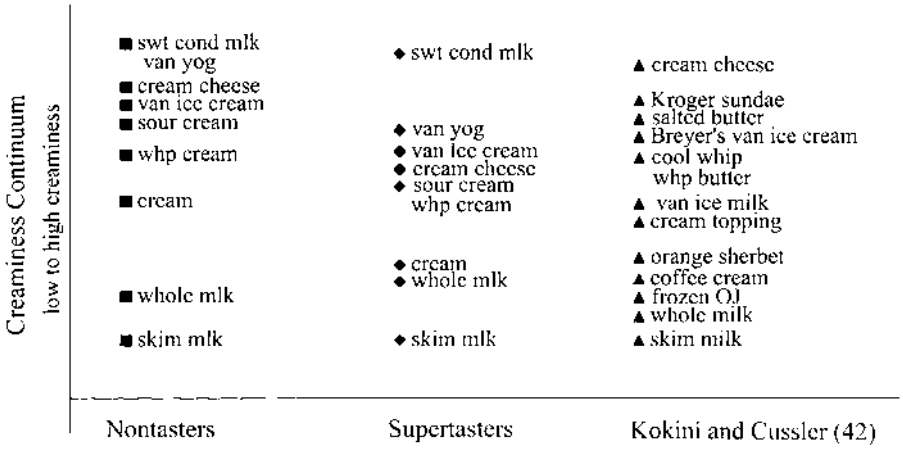

Figure 6 Relative comparison of product "ordering" for creaminess perception between dairy flavor/texture dimension of nontasters and supertasters from the free-choice profiling study and a regression model for creamines taken from Kokini and Cussler (42). Similar ordering of products was seen among the different groups regardless of PROP taster status. PROP, 6-*n*-propylthiouracil.

creaminess perception and rank ordering of products are similar across individuals regardless of PROP taster status. Thus, creaminess might be a universal construct that is independent of PROP status.

VII. CONSUMER RESEARCH

Heightened creaminess perception often equates with high consumer acceptability and perceived nutritional benefit (45). However, consumers are poor at describing creaminess, making it difficult to relate perception to liking. The aims of this consumer research study were (a) to understand how well PROP-classified consumers utilize sensory terminology (as derived from the FCP study) and (b) to assess the relationship of liking and creaminess perception among PROP-classified consumers.

The same nine dairy products were utilized as in the FCP study. Sixty-three nontasters and 51 supertasters from the PROP consumer pool were selected to participate in the study. All subjects were Caucasian women, ages 21–55, who regularly consume milk products (once or more

per week). The major descriptors from the FCP study were presented in a long list, and consumers selected/checked which of the terms applied to each sample. The list of words consisted of 8 appearance, 23 taste/flavor, and 17 texture/mouthfeel terms. Rating scales were also utilized. Creaminess intensity was evaluated by a 9-point intensity scale (1 = extremely weak and 9 = extremely strong). The samples were also assessed for overall liking, as well as for flavor and texture liking, by a 9-point hedonic scale.

Preliminary data showed that across all products, supertasters utilized a greater number of words from the check boxes than nontasters to describe the products. Supertasters used an average of 11.8 ± 0.2 [standard error of the mean (SEM)] terms, nontasters selected an average of 10.4 ± 0.2 terms [$F(1, 1024) = 29.31$, $p < 0.001$]. Results also showed that nontasters and supertasters used a similar number of appearance terms. However, supertasters selected more flavor and texture terms to describe the products. See Table 2 for a summary of results. These results confirm the findings of the free-choice profiling study.

Results from the rating scales were more difficult to interpret. Supertasters gave higher creaminess ratings across all samples [$F(1, 868) = 10.07$, $p \leq 0.02$]. Supertasters liked the flavor of all the products more than nontasters did [$F(1, 897) = 4.61$, $p \leq 0.03$]. However, results for overall liking were not statistically significant [$F(1, 897) = 3.063$, $p \leq$

Table 2 Comparison of the Use of Check-Box Terms for Appearance, Flavor, and Texture of Dairy Products by 6-*n*-Propylthiouracil-Classified Consumers[a]

	Appearance	Flavor	Texture
Sour cream		**	**
Vanilla yogurt		*	*
Whipped light cream		*	*
Skim milk			**
Sweetened condensed milk			*
Cream cheese			*
Whole milk		*	
Light cream			
Vanilla ice cream			

[a] Supertasters used a greater number of terms to describe the products at significance level indicated. *$p < 0.05$; **$p < 0.01$.

.08], and the observed trend was in the opposite direction than hypothesized. Thus, supertasters liked the products slightly more than nontasters, even though they found them more intensely creamy. It may be that taster groups utilize different cues in their perception, many of which may be important to their overall liking of the products. These data add to the debate surrounding the role of PROP status in liking of dairy products (22,23,35) and suggest the need for further study of this issue.

VIII. SUMMARY AND CONCLUSIONS

The present experiments revealed novel findings that deepen our understanding of the underlying cues for creaminess perception and the role of PROP taster status in individual differences in perception. First, both the FCP and consumer studies showed that nontasters and supertasters used different cues to judge creaminess. Supertasters utilized a larger lexicon of textural descriptors of dairy products. These findings imply that supertasters are more specifically sensitive to the textual components of dairy products. This finding supports previous research showing that supertasters are more sensitive to the oiliness of salad dressings and are better able to feel small particles placed on the tongue than nontasters (20,46). Ultimately, however, nontasters and supertasters gave similar overall rankings to the dairy products, suggesting that the integrated perception of creaminess is universal and not influenced by PROP sensitivity.

When subjects were asked to rate the intensity of creaminess on a scale, PROP supertasters gave higher creaminess ratings than nontasters, but the overall magnitude of the effect was small. This was shown in both the milk study and the consumer study. Thus, we conclude that PROP status exerts a stronger influence on individual descriptions of creaminess than on ratings of creaminess intensity and may explain why some previous studies did not find differences among PROP taster groups. A possible mechanism may be related to variation in tongue anatomical characteristics (11,20,27). Supertasters have more taste papillae innervated by trigeminal and other nerve fibers, which may produce a greater somatosensory sensation on the tongue.

This research also attempted to disentangle the contribution of appearance and sweetness to fat and creaminess perception. For supertasters, the addition of sweetness did not confound the effect of fat content on creaminess perception. Moreover, all subjects use appearance characteristics to evaluate products. However, when these characteristics

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were held constant, as in the sweet milk study, or removed from the analysis, as in the FCP study, differences between taster groups became evident. Thus, in situations in which subjects must rely on oral sensory cues to judge creaminess, supertasters would be expected to perform better than nontasters.

The relationship between liking of dairy products and PROP taster status remains unclear and requires further study. Textural defects such as gumminess, grittiness, and graininess reduce the acceptance of dairy products. It is conceivable that differences in liking of dairy products between supertasters and nontasters may relate to supertasters' heightened sensitivity to these qualities. This may be an important consideration when developing and optimizing new products in the food industry and should be investigated further.

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7

Genetic Basis for 6-*n*-Propylthiouracil Taster and Supertaster Status Determined Across Cultures

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I. INTRODUCTION

The ability to taste phenylthiocarbamide (PTC) and its chemical relative 6-*n*-propylthiouracil (PROP) is a well-known genetically determined human characteristic (Glanville and Kaplan, 1965; Krondl et al., 1983). Blakeslee and Fox (1932) first spoke of "different taster worlds" produced by individual variation in the sensitivity to bitterness of PTC and thereby stimulated enormous scientific interest in the genetic basis of taste perception. Phenylthiocarbamide studies across cultures flourished and PTC became entrenched in the contents of human genetics textbooks. Fischer (1971) recommended the use of the PROP in further studies because of its nonsulfurous odor and low toxicity level. The previous emphasis on the study of PTC, particularly in the field of human taste psychophysics, refocused on PROP.

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II. PHENYLTHIOCARBAMIDE/ 6-*n*-PROPYLTHIOURACIL GENETICS

Initially, the results of family studies as well as observations that taste sensitivity for PTC was bimodally distributed and that more people were tasters than nontasters suggested that the ability to taste these substances was conferred by only one gene and inherited as a dominant mendelian trait (Blakeslee and Salmon, 1931; Harris and Kalmus, 1950; Hoyme, 1955). Incomplete dominance (in which neither allele masks the presence of the other) and environmental determinants were suggested to account for inappropriate segregation within families (Das, 1956; Falconer, 1946; Merton, 1958; Martin, 1975; Ibraimov and Mirrankhimov, 1979; Jones and McLachlan, 1991). Kalmus (1958) was the first to suggest that homozygous and heterozygous PTC tasters may be different after confirming that tasters who had only taster siblings (and therefore were more likely to be homozygous for the dominant allele) had a lower average PTC taste threshold than did tasters who had at least one nontaster sibling. Reddy and Rao (1989) on reexamining the genetic properties of PTC taste thresholds, concluded that variability in this trait is controlled by a major locus with incomplete dominance as well as by a multifactorial component. Olson and associates (1989) studied 120 families and concluded the data fitted best a two-locus model in which one locus controls PTC tasting and the other locus controls general taste ability. Results of studies that identify two types of nontasters, those with a specific inability to taste PTC and those with more generalized deficits in gustatory abilities, appear to be consistent with this hypothesis (Frank and Korchmar, 1985). Reed and colleagues (1995) came to the same conclusion of incomplete dominance after investigating PROP threshold distributions for 1015 subjects. Using the method of assessing multimodality described by Maclean and coworkers (1976), they found that a trimodal distribution of PROP taste sensitivity was at least as likely as the taster–nontaster model and therefore consistent with an additive mode of transmission.

III. SUPERTASTERS

A method devised by Harris and Kalmus (1949) dominated early PTC studies. In this method, subjects were classified as PTC/PROP nontasters or tasters on the basis of threshold measurements using standardized solutions. Over time, the use of more sophisticated psychophysical techniques (see review by Bartoshuk, 2000) allowed suprathreshold measure-

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ments that led to the discovery of "supertasters," a subset of tasters who perceive the bitter intensity of PROP as extremely high (Bartoshuk et al., 1992; Bartoshuk et al., 1994). Again, incomplete dominance was suggested to account for the three taster groups, in which homozygous tasters (TT) are supertasters, heterozygous tasters (Tt) are medium-tasters, and homozygous nontasters (tt) are nontasters. If this is the case, then suprathreshold measurements could be used to classify individuals as homozygous or heterozygous for the dominant allele.

IV. SEX, ANATOMICAL CHARACTERISTICS, AND RACE EFFECTS ON PHENYLTHIOCARBAMIDE/ 6-*n*-PROPYLTHIOURACIL SENSITIVITY

Numerous studies have investigated the distribution of PTC/PROP taster status with respect to individual characteristics such as sex, age, tongue anatomical features and race or ethnicity (Whissell-Buechy and Wills, 1990). Certain subject characteristics and environmental factors can alter the phenotype for the ability to taste PTC and PROP. A modifier of the genotype–phenotype relationship is sex. Women are more likely to be tasters and can taste PTC at lower concentrations than can men (Blakesley and Salmon, 1931; Fernberger, 1932; Boyd and Boyd, 1937; Hartmann 1939; Falconer, 1946; Hoyme, 1955; Bartoshuk et al., 1994; Reed et al., 1995). However, PTC/PROP sensitivity is not a sex-linked trait. That PTC sensitivity may fluctuate over the menstrual cycle (Kaplan and Fischer, 1965; Bhatia, Sharma and Mehta, 1981) suggests a role for sex hormones in PTC sensitivity. Other possible explanations for sex effects include modifier loci that may lie on the X chromosome and the presence of autosomal genes that may be regulated by sex chromosomes.

Anatomically, supertasters have been found to have the most taste buds and fungiform papillae and nontasters to have the least (Reedy et al., 1993; Tepper and Nurse, 1997, Yackinous & Guinard, 2001). This is interesting in light of the suggestion by Olson et al. (1989) that among PROP-sensitive individuals, at least two groups are present: one with a specific sensitivity to PROP (supertasters) and another with high sensitivity to a wide range of sensory stimuli. It is possible that the sensitivity of the latter group may be due to higher taste bud density. Anatomical data also support the sex difference: women have more taste buds and fungiform papillae. Thus the finding that more women than man are tasters may be due to their greater taste bud density.

The genetics of PTC tasting has received remarkably extensive investigation in populations ranging from out-bred groups such as university students in large cities (Fernberger, 1932) to small, genetically isolated groups such as the Samaritans (Bonne, 1966). Variation in the number of nontasters and tasters across race has been commonly cited (Levine and Anderson, 1932; Parr, 1934; Boyd and Boyd, 1937) and is also is supported by modern studies (Sato et al., 1997; Guo et al., 1998). Past anthropological studies have estimated the proportion of PTC nontasters to be approximately 30% among Caucasians, 10% among Asians, and 5% among African populations (Parr, 1934; Barnicot, 1950; Allison and Blumberg, 1959; Kalmus, 1971). A review of more than 370 PTC studies by Guo and Reed (2001) highlighted significant differences among ethnic populations in the distribution of taster status. For example, a mere 1.3% of 79 Nicaraguans were PTC nontasters (Stefano and Molieri, 1976), in contrast with 66.7% of 114 Indian subjects (Agrawal, 1964). Variations between Indian populations have been reported in many studies. For example, Kameswaran et al. (1974), using threshold measurements with 375 South Indian students, reported that 21.6% were PTC nontasters compared to 30.1% for the Central Indian population (Sisodia and Rao, 1968). In more dispersed global regions, PTC nontasters were found to be widely variant: 42% for Australoids, 2% for Americans Indians, 31.5% for Europeans, 21.6% for Polish Jews, and 7.8% for Mongoloids (Saldhana and Becok, 1959). Sato and Sata (1989) found that 5.4% of 427 Japanese students were PTC nontasters. With the exception of one small group of Brazilian Indians (Kalmus, 1957), nontasters were found in every population studied (Guo and Reed 2001).

Interestingly, in more recent studies using threshold measurements, a high degree of consistency in PTC tasting has been reported among Japanese subpopulations. For example, Sato and colleagues (1997) found that 9.4% of 915 Japanese students were PTC nontasters. In other studies with Japanese, PTC nontasters constituted 12.5% of 1625 subjects in Sapporo (Matsunaga et al., 1954), 13.4% of 1021 in Chiba (Nakajima, 1959), 9.1% of 921 subjects in Osaka and Kyoto (Fukuoka, 1936), and 11.3% of 1169 subjects in the western districts (Ogawa, 1960).

Population variability in the ability to taste PROP has also been reported in several more recent studies. In one Indonesian study 1.2% were PROP nontasters (He, 1997), and Smagghe and Louis-Sylvester (1998) reported 73% nontasters among 173 French Caucasian females. Drewnowski et al. (1997) found that the distribution of PROP nontasters was 32% for Caucasian women, but only 11% for non-Caucasian women

in a study group of 159 women. In 2002 study, Pasquet and coworkers (2002) used threshold methods to assess the PROP status of 123 Tunisians (38 males, 85 females) with the result that 28.5% were low threshold tasters (supertasters), 59.3% were medium tasters, and 12.2% were nontasters. Reported variation in PROP sensitivity across racial groups corroborates the more abundant PTC evidence of the universality of the bimodal or trimodal distribution of PTC/PROP taster–nontaster status (Reed et al., 1995). These population similarities and differences in prevalence of nontasters suggest that understanding of the natural history of human populations might be advanced by measuring taster status in them.

V. LIMITATIONS IN COMPARING TASTER DISTRIBUTIONS ACROSS POPULATION GROUPS

One limitation in comparing PTC/PROP taster status distributions from various independent studies is that no standardized method of stimulus delivery and measurement was used across all the studies. In general, however, two methods have been widely used to determine phenotype of subjects for PTC/PROP status. One is the threshold method devised by Harris and Kalmus (1949), which involves determining the lowest detectable concentration of PTC or PROP. In the other method the suprathreshold intensity of PTC or PROP stimuli, either presented in solution or saturated and dried onto filter paper (Bartoshuk 1997), is rated. The most popular psychometric scale used to rate PTC/PROP intensity in recent years is the labeled magnitude scale (LMS) (Green et al., 1993). This quasi-log scale with semantic descriptors is equivalent to magnitude estimation scaling and prevents ceiling effects. In order to classify subjects into three taster groups, the PROP suprathreshold taste intensity of the individual is compared to his or her rating of a sodium chloride standard. When the two functions are superimposed, individuals whose slope of the PROP curve is much lower than the slope of the NaCl curve are classified as nontasters, whereas medium tasters have slopes that overlap. Supertasters have a steeper slope for PROP than for NaCl (Bartoshuk et al., 1992). Whereas the threshold method categorizes subjects into two groups, tasters and nontasters, suprathreshold methods have the advantage of segmenting the heterogeneous taster group into at least three subgroups (Reed et al., 1995, Bartoshuk, 2000).

In light of the clear sex effects in taster status distributions, another limitation in interpreting and comparing PTC/PROP distributions from

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previous studies is that the subjects were usually a mixed-gender group having unequal numbers of males and females. The relative proportions of males to females are likely to have skewed the distributions. This is because as the number of women increases in the sample group, so do the numbers of tasters and supertasters.

VI. THE UNIVERSITY OF NEW SOUTH WALES STUDIES

Over six years (1997–2002), several Australian studies conducted at the University of New South Wales (referred to hence as the UNSW studies) collected PROP data from different ethnic groups. As well as allowing investigation into ethnic group differences, that is, the pattern of the distribution of taster status across population groups, the results have shed light on the nature of the genetics of PROP taste sensitivity, as is outlined in the following brief account.

All the UNSW PROP studies used a standardized method of PROP stimulus delivery, common rating scales, and standardized taster status classification criteria. This method allowed valid comparisons of the PROP status distributions across the different ethnic groups as well as separation of data on gender. In all studies, dry "PROP papers" impregnated with 1.2 mg of PROP (Pfaltz-Bauer, Waterbury, CT) were used for stimulus delivery (Bartoshuk, 1997). Subjects were asked to place the paper on the tongue for 30 sec and then to rate its intensity by marking the LMS that had been translated from English into the language of the subjects (see Fig. 1a for the Japanese LMS; Fig. 1b shows for the cutoffs used to classify nontasters, mediumtasters, and supertasters, which were based on the work of Bartoshuk, 1997). Chi-squared statistical analyses were used to compare the distributions between groups with the level of significance at $p < 0.05$.

Table 1 shows the variation in the distribution of taster status across six ethnic groups. In agreement with previous studies, there are more tasters and supertasters in the Asian groups than in the Caucasian groups (Bell, Song, and Spehar, 2002; Wong, 2000; Bell and Song, 1999; Leung, 1998; Tong, 1998; He, 1997). It can also be seen from Table 1 that the UNSW studies agree with previous findings (Blakeslee and Salmon, 1931; Whissell-Buechy and Wills, 1990; Bartoshuk et al., 1994; Guo and Reed, 2001) that sex differences are commonly observed across populations (Bell, Song, and Spehar, 2002; Wong, 2000). Given this consistency,

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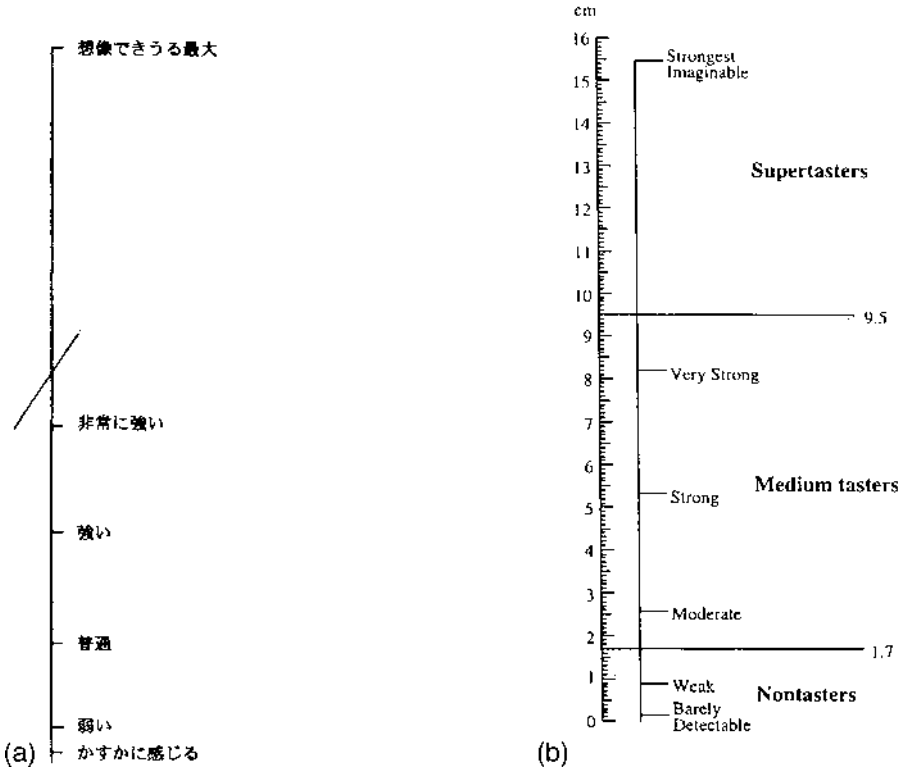

Figure 1 (a) Japanese labeled magnitude scale; (b) cutoffs used for taster status classification.

and to preclude the confounding effect of sex, same-sex comparisons are recommended in PROP studies in which cultural, racial, or ethnic variables are of interest.

In addition to the obvious variation in the distribution of PROP taster status across ethnic groups, closer analysis of the results from all the UNSW studies reveals a striking trend. As Fig. 2 shows, as the proportion of nontasters increased in the study group, the proportion of the supertasters *as a proportion of the taster group* (supertasters and tasters) decreased, and vice versa. Figure 3 shows the correlation ($r = -0.795$) between the proportion of nontasters in the study groups and the proportion of supertasters in the taster group, which clearly

Table 1 Distribution of 6-*n*-Propylthiouracil Taster Status Across Five Ethnic Groups (the University of New South Wales Studies)

Study group	*n*	NT[a], %	MT, %	ST, %	MT, % of T	ST, % of T
Australian (Bell, Song, & Spehar, 2002)	540	15.6	57.8	26.7	68.4	31.6
Caucasian Australian	317	21.8	59.6	18.6	76.2	23.8
Asian Australian	223	6.7	55.2	38.1	59.1	40.9
Australian (Wong, 2000)	577	13.7	52.5	33.8	60.8	39.2
Caucasian Australian	312	17.9	53.8	28.2	65.6	34.4
Females	144	12.5	54.9	32.6	62.7	37.3
Males	168	22.6	53	24.4	68.5	31.5
Asian Australian	108	9.3	43.5	47.2	48.0	52.0
Females	63	7.9	42.9	49.2	46.6	53.4
Males	45	11.1	44.4	44.4	50.0	50.0
Japanese females (Bell & Song, 1999)	224	3.6	46.9	49.6	48.6	51.4
Hong Kong females (Leung, 1998)	36	8.3	27.8	63.9	30.3	69.7
Singaporean females (Tong, 1998)	123	4.9	48.8	46.3	51.3	48.7
Indonesian females (He, 1997)	86	1.2	34.9	64.0	35.3	64.7

[a] T, taster; NT, nontaster; MT, medium taster; ST, supertaster.

illustrates this reciprocal relationship. Since previous cross-cultural studies with PTC did not measure supertasters, this relationship has not been reported in the PTC literature. Including supertaster measurement in these studies has revealed that populations with a large nontaster subgroup have a small supertaster subgroup, and vice versa. Thus, supertaster status is more prevalent in populations that have fewer nontasters. As this result is not an arithmetic illusion, how might genetics explain this finding?

This observation is consistent with a mode of inheritance for PROP tasting that is incompletely dominant, and therefore an additive mode of mendelian transmission. In this model, if there is a high proportion of nontaster alleles (tt) in the population, there are relatively more heterozygous mediumtasters (Tt) and fewer homozygous supertasters (TT). Conversely, if there is a low proportion of nontaster alleles (tt) in the

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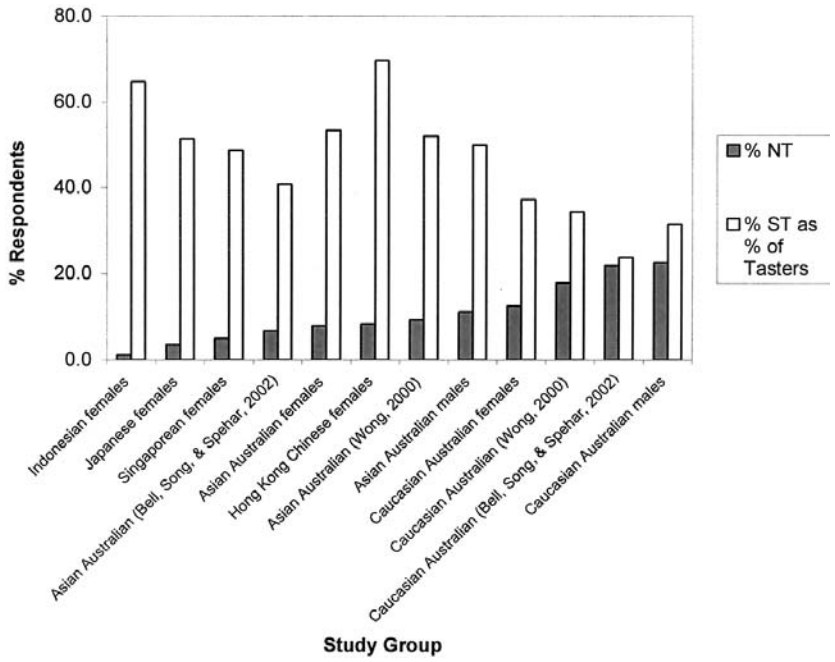

Figure 2 Comparison of the percentage of nontasters to the percentage of supertaster, (as a proportion of the tasters) for each study group.

population, there are relatively few heterozygous mediumtasters (Tt) and more homozygous supertasters (TT). Thus the observation that the proportion of nontasters in the population is inversely correlated with the proportion of supertasters in the taster group gives strong support to the incomplete dominance model of PROP inheritance and confirms supertaster status as a manifestation of two dominant alleles (TT). This model was foreshadowed by Kalmus (1958) and provides a genetic basis for the existence of supertasters as proposed by Bartoshuk and coworkers (1994).

VII. VALIDITY OF CROSS-CULTURAL COMPARISONS

There is ongoing debate about whether different cultures use psychometric rating scales differently (Prescott and Bell, 1995). However, the

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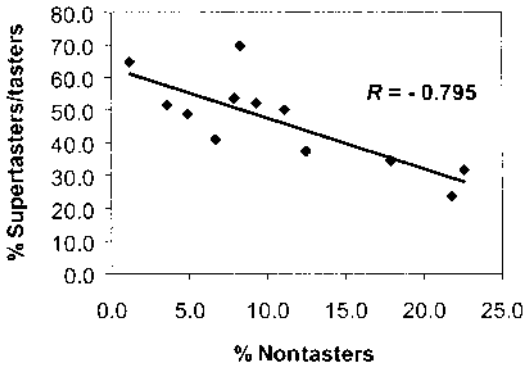

Figure 3 Inverse correlation between the proportion of nontasters and the proportion of supertasters from the taster group (medium tasters and supertasters).

agreement between the distributions found in the UNSW PROP studies using suprathreshold rating scales (LMS) and that of previously published studies that used threshold methods is a strong indication that cross-cultural scaling effects are negligible, particularly since the latter do not use scales at all. For example, the results from the UNSW suprathreshold data that show differences between Caucasian and Asian female taster distributions (see Table 1) agree with those of Drewnowski and associates (1997), who also found, by using threshold measures, that the distribution of PROP nontasters was 32% for Caucasian women but only 11% for non-Caucasian women. One might expect greater variation between such independent findings were the differences caused by, for example, a cultural propensity in one group to exaggerate scale responses. In addition, the broad dispersion of responses across the length of the scale within each group suggests that subjects are using the scales properly and that the observations are not merely due to systematic shifts along the rating scales by some groups. In addition, in several cross-cultural studies, no differences were found between Japanese and Australian consumers in their perception of the taste intensity of a selection of manipulated foods. When sweetness intensity was manipulated in ice cream, orange juice, and breakfast cereal, Japanese and Australian subjects gave almost identical ratings across the four sweetness intensities of each food (Prescott and Bell, 1995). This level of agreement suggest not only that the groups perceived the sweetness intensities similarly but also that all

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groups use the rating scales in much the same way. Furthermore, Laing and colleagues (1993), using suprathreshold measurement of differential sensitivity, found that Japanese and Australian subjects showed no differences in sensitivity to variations in sweetness, saltiness, sourness, and bitterness. Thus the convergence of data from cross-cultural suprathreshold sensitivity judgments and suprathreshold ratings, as well as previous studies showing no significant effect of culture in the use of scales (Prescott and Bell, 1995), suggest that rating the sensitivity to PROP reflects unbiased operations of perceptual mechanisms.

VIII. LANGUAGE AND LABEL DESCRIPTORS

Issues to consider in future cross-cultural PROP studies are which language and scales will be appropriate. Communicating effectively across different languages is crucial in any cross-cultural research. Language is critical in profiling sensory qualities, in terms of both sensory descriptors and methods (scales) used to measure them. A good practice is to test questionnaires by back translation to ensure linguistic coherence and easy communication.

Bartoshuk and coworkers (2003) suggest that the use of the LMS will be optimized by changing the descriptor at the top end of the scale to "strongest imaginable sensation of *any kind*," as opposed to the implied highest imaginable *oral sensation*. This ensures that the full range of sensations is the context in which subjects make a judgment, versus a context of taste sensations. The latter may not appropriately separate the three taster groups since the groups live in taste worlds of varying perceived intensities. Nevertheless, the LMS is an ideal multimodal scale, because it has both ratio properties and descriptors, which enhancing its psychometric quality and user-friendliness. In the early UNSW studies the most intense sensation of the scales was labeled "strongest imaginable" and was later modified to "strongest imaginable sensation (including pain)". A comparison of corresponding data (Wong, 2000, vs. Bell, Song, and Spehar, 2002 from Table 1) showed no significant difference between scale usage in terms of the distributions of taster, nontaster, and supertaster status. In addition, in future cross-cultural studies, comparison of data between expatriate groups with common ethnic origins, such as Asian Australians, will allow investigation of the strength, if any, of cultural factors on PROP perception.

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IX. HEALTH IMPLICATIONS OF ETHNIC VARIATION IN THE DISTRIBUTION OF TASTER STATUS

It has been suggested that PTC/PROP sensitivity might contribute to diet selection, independently of influences such as economics, culture, environment, and habit (Drewnowski et al., 1997; Bartoshuk, 1991, 2000). If this is so, differential distribution of bitter taste sensitivity across different ethnic groups may predispose whole populations to greater or lesser risk from unhealthy food choices. Can this possibly be so? It has been hypothesised that PTC and PROP tasters who have greater sensitivity to bitterness are more likely to avoid those bitter compounds often associated with toxic compounds, and nontasters are willing to eat a broader variety of foods. Drewnowski and Rock (1995) noted the clinical implications of rejection by PROP tasters of bitter foodstuffs containing phytoestrogens, indoles, and flavonoids useful for cancer prevention found in cruciferous vegetables. An early finding that patients with carcinoma of the cervix were more likely to be tasters was made by Milunicova and associates (1969). Tepper and Nurse (1998) suggested that lower taste sensitivity to PROP might serve as a marker for increased acceptance of and higher risks associated with dietary fat. There are also reports of associations between PTC taste status and diseases and traits not directly related to taste, which include dental caries (Chung et al., 1962), eye disease (Kalmus and Lewkonia, 1973), and thyroid disorders (Facchini et al., 1997). It remains unclear and a matter for more research to determine whether PTC/PROP sensitivity status influences food intake in individuals or in groups and whether PROP status has potential as a feeding behavior risk indicator for diet-related diseases (see review in Drewnowski, 2000).

X. CONCLUSIONS AND FUTURE DIRECTIONS

Cross-cultural PROP studies, which include supertaster measurements and use of common protocols, have confirmed previous observations made with PTC and have contributed some new insight into PROP/PTC genetics. We found there is considerable variability in the distribution of PROP taster status across ethnic groups. The proportion of nontasters and supertasters is much greater in Japanese and Indonesians compared to that of Caucasian groups. Sex differences in PROP sensitivity were confirmed across different ethnic groups, as there was a significantly greater proportion of females in the two taster groups (supertasters and medium tasters)

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than of males. Given robust sex and race effects, future investigations should assess same-sex and same-race subjects to deal with one variable at a time.

An inverse correlation was observed between the proportion of nontasters and the proportion of supertasters as a proportion of the tasters measured across several ethnic groups. This finding supports an incomplete dominance model for PROP inheritance and confers upon supertasters the genetic identity of individuals with two dominant alleles (TT). This finding has not been previously reported in PTC studies. It remains to be understood why in some human populations high or low base rates of tt or TT alleles have developed. The distribution of PROP taster status may be important in conferring certain health advantages on certain ethnic groups and deserves further study. The study of PROP taster status may also be of use in understanding human natural history as a means of exploring points of ancestral divergence or convergence between population groups.

Finally, additional family studies and characterization of the molecular basis for PROP, by mapping and cloning the PTC/PROP gene, are required for resolution of the mode of inheritance for PROP sensitivity and for better understanding of the origins of taster–nontaster differences. Until genetic studies can determine with certainty which subjects carry two copies of the dominant allele, cutoffs between medium and supertasters will remain indistinct.

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8

6-*n*-Propylthiouracil as a Genetic Taste Marker for Fat Intake, Obesity, and Chronic Disease Risk

Current Evidence and Future Promise

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I. INTRODUCTION

Taste blindness to the bitterness of thiourea compounds such as phenylthiocarbamide (PTC) and 6-*n*-propylthiouracil (PROP) is inherited (1). Approximately 30% of Caucasians in Western Europe and the United States can be classified as PROP/PTC nontasters. The other 70% are considered tasters and perceive these compounds as moderately bitter (medium tasters) or extremely bitter (supertasters) (2).

Since the chance discovery of this trait by A. L. Fox in 1931 (1), hundreds of research publications on PTC/PROP tasting have appeared in the literature. Numerous studies have documented the phenotypic frequency of PTC taste blindness in population groups around the world (3–5). Family studies and more recently molecular genetic studies have sought to understand how the trait is determined and inherited (6–8). Psychophysical studies have begun to identify key relationships between PTC/PROP taste sensitivity and individual variation in taste and food selection (9–11). These topics have been the subject of numerous reviews (12–17).

The possibility that PROP status is a predictor for eating patterns has stimulated considerable interest in this phenotype as a marker for

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diet-related chronic diseases such as obesity, cardiovascular disease, and some forms of cancer. If such a role exists, then PROP status could be an invaluable tool in epidemiological studies, which seek to identify relationships between diet factors and disease risk. Presently, our understanding of the associations between genetic taste factors and chronic disease is limited. Nevertheless, initial findings are supportive of this role and strongly encourage further investigation of these interactions.

This chapter critically reviews and evaluates current findings about the associations between PROP status and diet-related chronic diseases with special emphasis on the links between fat intake and obesity. Obesity, as have other complex diseases, has numerous genetic, environmental, and behavioral determinants (18). Until recently, PROP studies have focused almost exclusively on univariate relationships—establishing associations between PROP status and a single outcome variable such as body weight or cancer risk (19,20). These simple analyses ignore the multidimensional nature of diet–disease relationships. In most cases, the reported associations have been weak or inconsistent and as such, subject to criticism (see Chapter 11 in this volume). 6-*n*-Propylthiouracil status may interact with a variety of mediating variables, which could alter its influence on eating behavior and disease risk, and these variables have mainly been overlooked in the published literature. The viewpoint advanced in this chapter is that mediating variables may be critical for interpreting associations between PROP and disease risk. Identifying the relevant variables and incorporating them in future studies are expected to strengthen the associations between PROP and disease considerably as well as fill important gaps in our understanding of the causes of chronic disease development. A major focus in this laboratory is on identifying mediating variables, and several of them are described in the following sections.

II. 6-*n*-PROPYLTHIOURACIL STATUS, DIET, AND CHRONIC DISEASE RISK

Figure 1 is a simple flow diagram illustrating the associations between PROP status and chronic disease risk. According to the diagram, PROP status influences taste perception and food acceptance, which in turn influence diet. Dietary patterns could influence disease risk through two general

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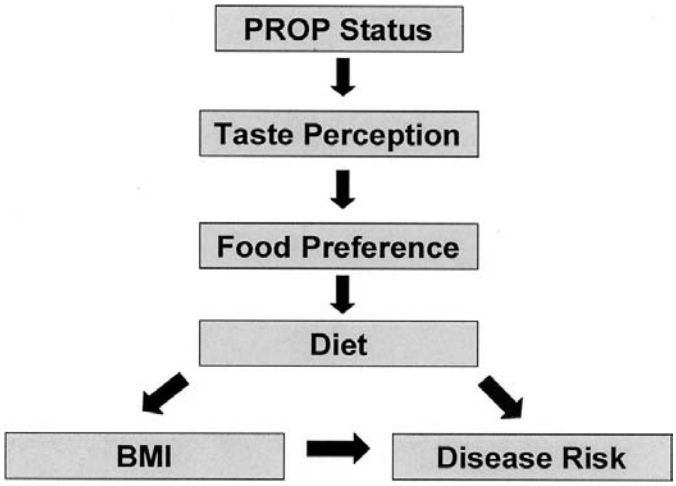

Figure 1 Flow diagram showing the relations among PROP status, diet, and chronic disease risk. PROP, 6-*n*-propylthiouracil; BMI, body mass index.

pathways. One pathway relates changes in a specific dietary parameter to chronic disease risk. For example, one well-established pathway relates high intakes of alcohol to increased risk of cancers of the esophagus, liver, and breast (after menopause) (21). Another pathway relates increased energy intake to the development of obesity, which heightens the risk of cancers of the esophagus, colorectum, breast, and endometrium (21), as well as the susceptibility to other chronic diseases such as diabetes, cardiovascular disease, and stroke (22). A comprehensive summary of dietary risk factors for chronic disease is beyond the scope of this chapter; individual topics have been reviewed elsewhere (21,23–26).

Using this model, we have developed a set of hypotheses linking PROP status with obesity and chronic disease risk (27). It is hypothesized that PROP nontasters are less responsive to the oral sensation of fat and prefer high-fat foods. Over time, greater consumption of a high-fat diet by nontasters could lead to increased weight gain and obesity in these individuals, increasing their susceptibility to obesity-related diseases. This model assumes that PROP status serves as a dietary marker for obesity and does not imply a direct, causative role for this phenotype in the de-

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velopment of obesity. Although such a role is not ruled out, current evidence does not support this argument. Data supporting each stage of the model are presented in the following sections.

III. 6-*n*-PROPYLTHIOURACIL, FAT PERCEPTION AND FAT ACCEPTANCE

A handful of studies have examined the associations between PROP status and perception and acceptance of high-fat foods, and results are inconsistent. Findings range from strong support for this association (28–30) to weak or no support for this relationship (31,32). However, emerging data shed considerable light on these contradictions, and a number of important themes have developed from this work.

Since dairy products offer a convenient medium to manipulate fat content, a number of studies have investigated PROP-related differences in fat perception using this stimulus. Duffy and associates (30) (also see Chapters 1 and 10 in this volume) found that supertasters perceived more creaminess in fluid dairy products at fat concentrations in the range of 11% to 54%. Two subsequent studies (31,32) did not confirm the results of Duffy and associates (30), calling into question the accuracy of the earlier findings. However, certain design features of the latter experiments might have contributed to the discontinuity in findings. The Drewnowski and coworkers study (31) tested a large sample set consisting of 15 mixtures of milk and cream, which also varied in sucrose content. All samples were evaluated in a single session. Yackinous and Guinard (32) used a two-by-two design to vary both the fat content and the flavor of chocolate drinks and pudding samples, but over a very narrow range. Both studies put a high demand on subjects to discriminate among complex samples with strong carryover effects. These design features probably contributed to a lack of robustness in these experiments.

However, more recent data suggest that design considerations are probably not the primary source of the conflicting results. In a series of experiments, Kirkmeyer and Tepper (see Chapter 6 in this volume) utilized a milk model system varying in fat content (0%–30%) and sweetness (0% or 6% sucrose) or commercial dairy products to investigate differences in creaminess perception between PROP nontasters and supertasters. In experiments in which subjects were asked to rate creaminess intensity on a scale, supertasters gave higher creaminess ratings to the samples than non-

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tasters, but the magnitude of the effect was small. The fundamental difference between nontasters and supertasters was the manner in which the two groups described dairy products. When asked to describe commercial dairy products with a personalized list of descriptors, supertasters utilized a complex lexicon and depended more heavily than nontasters on dairy-derived flavor and texture attributes to make their assessments (e.g., rich, buttery, creamy, dairy, heavy, mouthcoating). In contrast, nontasters depended on simple texture terms and basic tastes (e.g., thick, milky, sweet, sour).

Kirkmeyer and Tepper concluded that PROP status exerted a stronger influence on the qualitative aspects of creaminess perception than on quantitative judgments of creaminess intensity; in other words, supertasters utilized more attributes to judge creaminess. This difference had only a modest effect on ratings of creaminess intensity. This finding might explain why some studies did not discover differences in creaminess perception among PROP taster groups.

Using a different stimulus, Tepper and Nurse (28) had previously found that tasters, especially supertasters, were more adept at discriminating high- from low-fat salad dressings. This effect was quite robust and related to the oiliness of the samples. 6-*n*-Propylthiouracil tasters have a greater density of fungiform papillae on the anterior of the tongue (28,33) and are presumed to have more trigeminal and other somatosensory input. Since these fibers are associated with touch and pressure sensitivity on the tongue (34,35) (also see Chapters 1, 4, and 10 in this volume), PROP tasters may have an advantage in judging the oral sensation of fat in this medium.

Some earlier studies reported that PROP nontasters gave higher acceptance ratings than tasters to intensely sweet or bitter-tasting stimuli (36,37), and a similar relationship was expected for fat-containing stimuli. Accordingly, in the Tepper and Nurse study (29) on salad dressings, 72% of the nontasters preferred the high-fat salad dressing, whereas only 28% of this group preferred the low-fat salad dressing. In contrast, medium tasters and supertasters found the samples equally acceptable.

Other studies have reached a similar conclusion regarding heightened preferences for fat among nontasters, but these experiments also suggested an additional influence of gender on liking responses. For example, Keller and colleagues (11) showed that in preschool children, nontaster girls gave higher acceptance ratings to full-fat milk samples than did taster girls or boys in either taster group. An earlier study by Duffy and coworkers (19) also found a gender difference in reported food preferences as a function of PROP status. Among women, PROP bitterness intensity

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was inversely correlated with self-reported preferences for high-fat foods such as meats, dairy foods, salad dressings, spreads, and sweet snacks. Thus, nontaster women liked these foods more than taster women. However, men showed the opposite responses. For men, liking ratings positively increased with PROP bitterness intensity. Whether these differences reflect a true gender dichotomy or the influence of cognitive factors that covary with gender has yet to be determined. As discussed later, studies relating PROP status to dietary intake and body weight suggest that cognitive variables may play a role in these interactions.

IV. 6-*n*-PROPYLTHIOURACIL AND DIETARY FAT INTAKE

Keller and associates study (11) described previously also used a food frequency questionnaire (completed by mothers) to assess habitual dietary intake of the children. Results showed that nontaster children reportedly consumed two to three more servings of discretionary fats per day (i.e., salad dressing, butter/margarine, mayonnaise) than taster children. This difference was primarily due to nontaster girls, who consumed more servings than the other groups. To our knowledge, this is the first study linking PROP status with variation in dietary fat intake in any age group, and the results fit well with the earlier findings of Tepper and Nurse (29) showing greater acceptance of high-fat salad dressing by nontasters.

Subsequent studies in PROP-classified children revealed that other dietary patterns may be relevant as well. In another group of children drawn from the same study population, Keller and Tepper (39) found that nontaster children reportedly consumed more high-fat meats, whereas taster children reportedly consumed more sweets and snacks such as soft drinks, juices, candy, cakes, and cookies. No differences in discretionary fat intakes were observed in the second study, a finding that is difficult to reconcile with our previous work (11). Nevertheless, both studies identified fat-related dietary patterns that distinguished taster and nontaster children. The significance of these differences is not yet known since foods in any one of these dietary patterns (meats, sweets and snacks, discretionary fats) could theoretically lead to excess energy intake and weight gain if they were habitually overconsumed. Although we were unable to link a particular dietary pattern to higher energy intakes in any of the groups of children we studied, it is conceivable that such differences could develop over time. This possibility will be addressed in future studies.

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V. 6-*n*-PROPYLTHIOURACIL AND BODY WEIGHT—THE IMPORTANCE OF MEDIATING VARIABLES

The idea that food intake and body weight may be associated with PROP status arose from the work of Roland Fischer and his colleagues in the 1960s. While conducting studies on PROP thresholds, Fischer, Griffen, and Rockey (40) noted that tasters tended to be endomorphs, manifesting a thin and angular body type, whereas nontasters tended to be ectomorphs, manifesting a more fleshy body type. Studies on food preferences conducted at the same time by Fischer's group (41) and others (42) revealed that tasters had more food dislikes than nontasters, particularly for sharp- and bitter-tasting foods such as black coffee, ales, strong cheeses, and cruciferous vegetables. Many subsequent studies focused on avoidance of thiourea compounds in cruciferous vegetables since these substances were known to have antithyroid properties that have well-recognized effects on nutritional state (43–46). Curiously, the possibility that PROP taste blindness could affect general eating patterns that could predispose an individual to excess weight gain and obesity was not actively pursued for another 30 years.

In 1995, we began a series of studies investigating associations between PROP status and fat acceptance and body weight. Our interest in this question arose from a chance observation in our study on fat perception in salad dressings discussed previously (28). As reported in Tepper and Nurse (29), results showed a small, negative association between PROP status and body mass index (BMI) among male subjects. This finding was intriguing because nontasters in that same study also preferred high-fat salad dressing. These data provided preliminary, albeit indirect evidence that variation in body weight among PROP taster groups might reflect differences in acceptance of fat. Results from this study and several subsequent studies are discussed later and are compiled and presented in Fig. 2 (27,29,39).

A. Young Adults

Tepper and Nurse (29) reported a modest effect of PROP status on BMI among males, but no effect among females (see Fig. 2b). In recruiting subjects for this study, we adhered to the convention of eliminating overweight subjects to minimize bias in the sensory ratings. Previous studies had reported a positive association between body weight and hedonic ratings to

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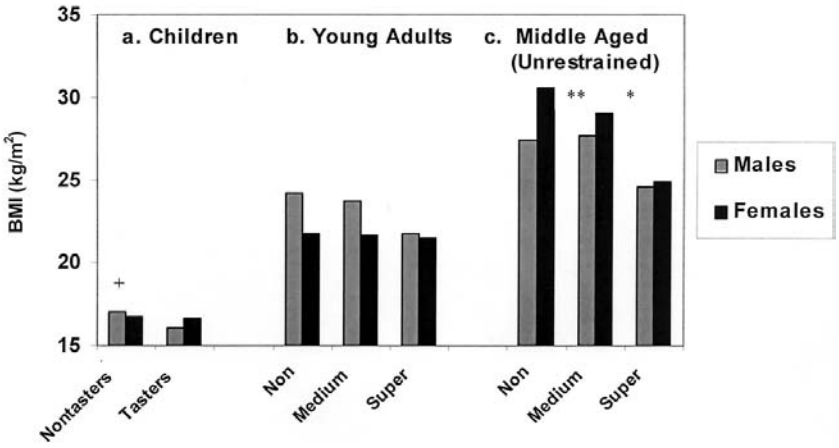

Figure 2 Influence of PROP status on BMI in three experiments. a. Preschool children: nontaster boys had higher BMIs than taster boys ($^{+}p \leq 0.05$); b. young adults: no significant differences in BMI were observed; c. middle-aged men and women who were unrestrained eaters: both nontaster women and medium taster women had higher BMIs than supertaster women ($^{**}p \leq 0.01$; $^{*}p \leq 0.05$). No significant differences were found among men. Data are not shown for restrained eaters. PROP, 6-*n*-propylthiouracil; BMI, body mass index. (*Source*: Data adapted from Refs. 27 and 29.)

sweets and fats (47,48). However, studies on body weight need to include overweight and/or obese individuals to provide enough variation in body weight to detect group differences. These conflicting objectives make a typical taste study a poor context in which to study body weight differences. This factor may explain why several taste studies did not find differences in body weight among PROP-classified groups (19,20,31,32,49). As discussed later, Tepper and Ullrich (27) subsequently showed a strong negative association between PROP status and BMI among middle-aged women manifesting a wide range of body mass indices (BMI range, 19–36).

B. Middle-Aged Adults

The lack of association between PROP status and BMI among young women in the Tepper and Nurse (29) study suggested that some other factor, perhaps gender-related, might have weakened or abolished this relationship. Previous research had shown that dietary restraint (the conscious

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control of eating) and disinhibition (loss of control over eating) are strong determinants of food intake and body weight in women. Women who score high on dietary restraint typically show reduced preferences for high-fat foods (50–53). In addition, women who score high on disinhibition have a higher BMI than those who score low in this characteristic (54–56). We reasoned that restrained eaters would be more strongly motivated by weight concerns than by taste in the selection of the foods they eat. Thus the relation between PROP status and BMI should be evident only among women with low dietary restraint.

Tepper and Ullrich (27) tested this hypothesis in a study involving 86 middle-aged women recruited from the community. Data were adjusted for disinhibition since this variable was found to have a strong, positive influence on BMI that was independent of PROP classification. Figure 2c shows the BMI results for women with low dietary restraint after adjusting for disinhibition. Nontasters and medium tasters had significantly higher BMIs than supertasters, and the magnitude of the group differences was large. Nontasters and medium tasters had adjusted BMIs that were six units and four units higher, respectively, than those of supertasters. As expected, no association was found between PROP status and adjusted BMI in women with high dietary restraint (data not shown).

We have also begun constructing a similar data set for middle-aged men (Tepper & Ullrich, unpublished observations), and to date, 35 men have been studied. Although men are less likely to be restrained and disinhibited eaters than women, a similar pattern emerged in men. Among men with low dietary restraint, nontasters and medium tasters had a marginally higher BMI than supertasters (see Fig. 2c). However, these differences were not statistically significant and may partially reflect reduced power to detect differences with a small sample set.

C. Preschool Children

Studies in young children suggested that the inverse relation between PROP status and BMI among males might have its origins in childhood. Preliminary findings reported by Keller and Tepper (39) revealed that nontaster boys had a higher BMI than taster boys. This pattern was not detected among the girls (see Fig. 2a).

D. Summary

Two general conclusions can be drawn from these data. First, the association between PROP and BMI begins to emerge in early childhood, and

this effect becomes progressively larger across age categories. This interpretation is consistent with our hypothesis that PROP status influences the development of eating habits early in life and that once established, these eating patterns have a cumulative effect on body weight across the life cycle. This conclusion finds further support in the findings of Lucchina and associates (57) (also see Chapter 10 in this volume), who also found an inverse association between PROP status and adiposity in elderly women. These findings need to be corroborated with prospective studies; if found reliable, they could have important implications for tracking the progression of weight gain and obesity across life stages.

Second, across all studies, the influence of PROP status on BMI was more consistently observed in males than in females, and this difference probably reflects the additional impact of cognitive factors on food intake and body weight variability in women. When we controlled for cognitive variables in the study in middle-aged women, large differences in BMI were observed among taster groups. Data from other types of studies suggest that the eating habits of women are more susceptible to environmental influences than are those of men. For example, van den Bree and associates (58) studied the eating habits of twins and showed that environmental factors (such as dieting) made a greater contribution to the eating patterns of females, whereas genetic factors made a greater contribution to eating patterns of males. Taken together, these studies suggest that the relative contributions of genes and environment to the expression of food habits and body weight may be gender-specific. Further characterization of these roles seems warranted.

VI. 6-*n*-PROPYLTHIOURACIL, OBESITY, AND CHRONIC DISEASE

A. Obesity

Studies have not yet been reported on the association between PROP status and body weight among obese (BMI > 30) or morbidly obese (BMI > 40) populations. Whether PROP status associates with extreme forms of obesity, which may have different underlying causes, remains to be tested. A more critical issue is whether PROP status associates with abdominal obesity, which carries the greatest negative health risk (22). Contradictory findings have recently been reported on PROP status and waist/hip ratio in moderately overweight populations (see Chapters 9 and 10 in this volume), suggesting the need for additional study of this question.

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Socioeconomic status, ethnicity, and age are well-known predictors of body weight. Whether the influence of PROP status remains after controlling for these factors is a controversial issue. Drewnowski (see Chapter 9 in this volume) studied a large clinical sample of 340 women consisting of recently diagnosed breast cancer patients and controls. He reported no influence of PROP status on BMI in a regression analysis after controlling for age. Contrasting results occurred in a study by Duffy and coworkers (see Chapter 10 in this volume), which found significant independent effects of age, gender, and PROP status on BMI in a large convenience sample of adults. Although the percentage of variance in BMI explained by the model was modest (adjusted $R^2 = 0.24$), it was in line with the results of other studies investigating the influence of sociodemographic and behavioral factors on adiposity (59).

B. Cardiovascular Disease

Duffy and colleagues have recently begun studying the association between PROP status and plasma lipid profiles (see Chapter 10 in this volume). Initial findings from two studies suggested that lower PROP bitterness (nontaster status) was associated with greater cardiovascular risk as measured by an elevated total cholesterol-high-density lipoprotein ratio (TC/HDL ratio). These provocative findings must be interpreted with caution. One study investigated a small sample ($n = 32$) of young men and women with normal lipid profiles. As a result of gender differences in the lipoprotein fractions, men typically maintain less desirable lipid profiles than women of childbearing age (60). Since the nontaster group was composed predominantly of men and the supertaster group was composed predominantly of women, gender differences might have confounded the results.

C. Diabetes

The relationship between PROP status and diabetes has not been intensively studied and remains uncertain. Nevertheless, a few studies have reported a higher prevalence of nontasters among both type 1 and type 2 diabetics (61,62).

Individuals with diabetes experience reduced sweet taste perception and higher preferences for sweet foods as compared to controls (63–66). Somewhat analogous findings have also been reported for PROP-classified individuals. For example, Looy and Weingarten (36) showed that

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PROP nontasters found sucrose less intense and were more likely to be sweet "likers." Tasters, on the other hand, found sucrose more intense and were more likely to be sweet "dislikers." Thus, it is possible that the PROP phenotype is a marker for sweet taste that is also associated with diabetes.

6-*n*-Propylthiouracil status may also relate to type 2 diabetes via a mechanism related to body weight. Obesity is a major risk factor for type 2 diabetes (22). Assuming that PROP status is a marker for obesity, then it may also serve as a predictive marker for the future development of type 2 diabetes. Although highly speculative, these provocative hypotheses deserve further study.

D. Cancer

Only one laboratory has examined the relations between PROP status and eating habits and cancer, and this work has focused exclusively on breast cancer (20) (also see Chapter 9 in this volume). These studies have consistently reported a modest association between PROP status and fruit and vegetable selection in women. However, no association between PROP status and incidence of breast cancer has been found (20). Although the role of PROP status in cancer risk appears tentative at present, additional data are needed to confirm current findings. 6-*n*-Propylthiouracil status has not been studied in connection with other diet-sensitive cancers, and such work offers additional avenues of future research.

VII. 6-*n*-PROPYLTHIOURACIL AND OTHER RISK FACTORS

A major goal of nutritional epidemiology is to assess relationships between risk factors and health outcomes. Risk factors for diet-related chronic illnesses include genetic disease markers (when they are known) and behavioral variables such as physical activity, alcohol consumption, and smoking. However, there is an ongoing need to identify better behavioral markers. Those that are reliable predictors and easy to measure are highly desirable. Both alcohol and the nicotine in tobacco have distinctive sensory qualities, including bitterness and irritation (2,9,67), which play a key role in the acceptance of these products. As described later, if PROP status correlates with the acceptance of these products, it could serve as a convenient indicator or proxy for use of alcohol and nicotine.

A. Alcohol

Alcohol has variable effects on disease development. As mentioned previously, excess alcohol intake is associated with greater risk of cancers of the esophagus, liver, and breast (21). However, moderate consumption of alcohol is a negative risk factor for cardiovascular disease (26). Alcohol also stimulates the appetite and increases overall energy intake through mechanisms that remain poorly understood (68–70). Thus, high alcohol intake could conceivably affect body weight gain and the risk of obesity, constituting another pathway for disease risk.

Some studies have shown that PROP tasters perceive more bitterness of and irritation from ethyl alcohol (2,9) (also see Chapter 4 in this volume), and they also exhibit lower preferences for bitter-tasting ales (42) and beer (71). Mela (72) showed that solutions of isohumulones were more intensely bitter to PROP tasters, but this effect was not replicated in beer. Other work has shown that PROP tasters consume fewer alcoholic beverages per year than nontasters (see Chapter 10 in this volume). These experiments, along with findings reported by Ullrich and Tepper (73) described later, seem to suggest a role for PROP status in the acceptance and consumption of alcoholic beverages. More data are needed to confirm current observations.

Earlier experiments suggested that PROP nontasters might be at greater risk for alcoholism because they lacked an aversion to the sensory characteristics of alcohol (74). But a subsequent study did not support this argument (75), and another study drew the opposite conclusion (76). Since the cause of alcoholism is poorly understood at present, further study of the role of PROP status in alcohol use and abuse seems warranted.

B. Smoking

Kaplan, Glanville and Fischer (77) showed that heavy smokers were significantly more likely to be nontasters. These findings were confirmed in a 2001 study by Enoch and coworkers (78), who found a higher percentage of nontasters among smokers even after controlling for the effects of smoking on taste. Moreover, the proportion of nontasters to tasters in nonsmokers was 1:3, whereas this proportion was 1:1 in smokers.

Tepper and Jackson (unpublished observations) analyzed data from 502 subjects who had participated in PROP-tasting studies in this laboratory for whom smoking information was available. Because only 20% of our subject population had a history of smoking (either current or

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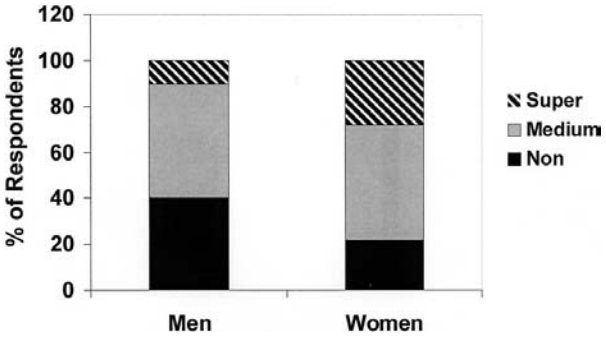

Figure 3 Proportion of men and women with a history of smoking as a function of PROP status. PROP, 6-*n*-propylthiouracil.

past), the statistical power of the analysis was limited. For this reason, we examined the relative proportion of nontasters, medium tasters, and supertasters among those with a positive history of smoking. Data were compiled separately for men and women.

Figure 3 shows that among male smokers, 40% were nontasters whereas only 10% were supertasters. These proportions varied slightly but not significantly from the frequency of nontaster and supertaster males in our study sample (35% nontaster males and 17% supertaster males). Thus, among males, smokers were slightly underrepresented among supertasters. In contrast, the frequency of smoking in women matched the frequency of the PROP phenotype in the female population. Our findings were in the hypothesized direction but less robust than those reported previously.

VIII. 6-*n*-PROPYLTHIOURACIL AND PERSONALITY FACTORS

Personality factors are well-known determinants of food choice. Food neophobia—the avoidance of novel foods—is associated with lower preferences for spicy foods and alcohol (79,80). In contrast, variety or sensation seeking (81,82) is related to higher preferences for chili peppers and caffeine (83). The extent to which personality factors may interact with PROP status to influence food preferences has been little studied.

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In 2001 Ullrich and Tepper (73) examined the influence of food adventurousness on preferences for bitter fruits and vegetables, alcoholic beverages, and pungent condiments. *Food adventurousness* is defined as the reported frequency of trying unfamiliar foods on a scale ranging from "never" to "most of the time". On this scale, 232 PROP-classified consumers were characterized as food adventurous or not food adventurous. Participants also completed a food checklist, indicating whether they liked or disliked 65 food items.

Results showed that food adventurousness had a robust effect on food preferences of PROP tasters but virtually no effect on those of nontasters. Food adventurous tasters liked significantly more fruits, vegetables, alcoholic beverages, and pungent condiments (including salsa, hot sauce, raw onions, and garlic) than tasters who were not food adventurous (see Table 1). Nontasters liked most of the foods regardless of whether they

Table 1 Liking of Vegetables, Fruit, Alcohol, and Condiments by Food Adventurous and Non–Food Adventurous 6-*n*-Propylthiouracil Tasters[a]

Food group	Food subgroup	*P* value[b]
Vegetables	Turnips, greens, endive, radishes	***
	Cooked carrots, cooked broccoli, raw cabbage	**
	Total	***
Fruit	Grapefruit; grapefruit, cranberry, and grape juice; oranges	**
	Strawberries, peaches, bananas	*
	Total	**
Alcohol	Dry red and white wine	***
	Rosé wine, wine coolers	NS
	Gin, bourbon	**
	Dark beer	**
	Total	***
Condiments	Green, black, and Greek olives; anchovies	*
	Sour pickles, sauerkraut, raw garlic, and onions	**
	Hot peppers, hot sauce, salsa	**
	Total	***

[a] Comparison of the number of foods liked per food subgroup for food adventurous and non–food adventurous PROP tasters. PROP, 6-*n*-propylthiouracil; NS, not significant.
[b] More foods per subgroup were liked by food adventurous PROP tasters at the significance level indicated.
*p <0.05; ** <0.01; *** <0.001.

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were food adventurous or not. Overall, the total number of foods liked was comparable in food adventurous tasters and both nontaster groups. Only tasters who were not food adventurous liked fewer foods overall.

These data suggest PROP tasters who are also food adventurous behaved more similarly to nontasters in that they reported liking a wide range of foods. Thus, only PROP tasters who were not food adventurous showed the hypothesized dislike of bitter and pungent foods. Mattes (see Chapter 11 in this volume) concluded that PROP status plays a minimal role in food selection behavior since the majority of studies reported only weak or null effects. However, earlier studies did not characterize subjects by food adventurousness. Assessing the interactive effects of PROP status and food adventurousness on food acceptance might lead to a better understanding of food selection patterns that link to disease outcomes.

IX. 6-*n*-PROPYLTHIOURACIL AND CHRONIC DISEASE RISK—A MULTIFACTORIAL MODEL

It had generally been assumed that PROP status exerts its influence on food intake, body weight, and disease outcomes through a simple linear pathway. However, data reviewed here challenge this assumption and argue that the emerging picture is far more complex than originally realized. Figure 4 conceptualizes these interrelationships in a multifactorial model.

Accumulating evidence supports a role for PROP status in the control of body weight that is mediated through changes in food selection. The specific dietary patterns that give rise to these differences in body weight are not well understood at this time. However, potential links have been identified between PROP status and intake of discretionary fats, meats and dairy, and sweets and snacks, and these relationships require further study. Cognitive factors such as dietary restraint and disinhibition may modify the relation between PROP status and weight by influencing eating attitudes and behavior.

There is limited evidence suggesting that PROP status influences smoking and alcohol consumption, which are known to modify chronic disease risk. In addition, these actions also influence body weight, and that influence may represent another pathway by which PROP status could link to obesity and risk of chronic disease. Finally, personality factors such as food adventurousness may interact with PROP status to modify overall energy intake or intake of specific dietary components (such as alcohol). The current model incorporates several key variables and relationships

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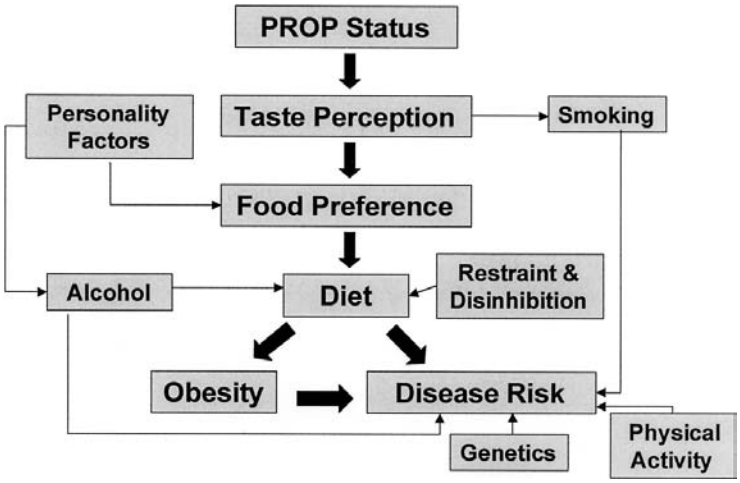

Figure 4 Multifactorial model of the relations among PROP status, dietary intake, and chronic disease risk. PROP, 6-*n*-propylthiouracil.

that have been identified in our work. Additional mediating variables probably exist, and these need to be identified in future experiments.

X. SUMMARY AND FUTURE DIRECTIONS

Current observations provide a rich source of data to begin formulating and testing hypotheses that may ultimately lead to greater insights into the causes of chronic disease. However, this work is still in its infancy, and many more studies have to be done before critical gaps in our understanding of the role of this phenotype in disease pathways can be resolved. Nevertheless, several research directions can be proposed. Well-designed population-based studies are needed to assess the influence of PROP status on diet–disease relationships critically. Given the complexity of human eating behavior, it is important that these studies incorporate measures that will permit a comprehensive analysis of the relevant variables. Prospective study designs will be especially valuable for determining the role of this phenotype in the development of eating habits in childhood and adolescence.

Another approach is to study genetically isolated so-called founder populations. The 1400 inhabitants of the village of Carlantino in south-

ern Italy can trace their ancestry to six founding couples. The members of this community take part in an ongoing study investigating the influence of genes on multifactorial disease outcomes. The current database contains complete health histories, clinical chemical values, and deoxyribonucleic acid (DNA) from all current residents. Birth registries are available from the 17th century. We are currently screening residents for PROP taster status. By minimizing genetic and environmental "noise" that is typically present in population studies, this project will provide a much clearer understanding of the influence of this phenotype on diet and disease outcomes.

Finally, all published studies attempting to link PROP status with dietary habits have utilized food records or intake questionnaires (11,19, 20,49), and reporting bias is a well-known limitation of such methods (84). Other approaches that do not depend on subjective reports such as laboratory feeding studies need to be utilized. Preliminary observations from food selection experiments in PROP-classified children suggest that pursuing this strategy will be useful (Bell & Tepper, unpublished observations).

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6-*n*-Propylthiouracil Sensitivity, Food Choices, and Food Consumption

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I. INTRODUCTION

Abnormal or extreme bitterness tends to be equated with dietary danger (Rousseff, 1990; Drewnowski and Gomez-Carneros, 2000). Conditioned through evolution to avoid bitter plant alkaloids and other toxins, humans reject foods that are perceived as excessively bitter (Hladik and Simmen, 1996; Drewnowski and Gomez-Carneros, 2000). The instinctive rejection of bitter taste, most pronounced among children and pregnant women, was at one time critical to survival. One possible explanation for the persistence of 6-*n*-propylthiouracil-(PROP)-tasting genes in humans is the genetic advantage of being able to detect and avoid bitter poisons (Boyd, 1950). Studies have linked genetic sensitivity to phenylthiocarbamide (PTC) and PROP with a dislike of other bitter tastes and with more aversions to bitter-tasting foods (Glanville and Kaplan, 1965; Fischer et al., 1961, 1984; Forrai and Bankovi, 1984).

Individual differences in bitter-taste sensitivity may influence dietary exposure to selected vegetables and fruit (Drewnowski and Rock, 1995). Among biologically active compounds present in citrus fruit, soybeans, *Brassica* species vegetables, green tea, and red wine are phenols, tannins, flavonoids, isoflavones, and glucosinolates (Drewnowski and Gomez-Carneros, 2000; Fenwick et al., 1983; Rousseff, 1990). These compounds are reported to have antioxidant and anticancer properties and play a

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major role in dietary strategies for chronic disease prevention (Steinmetz and Potter, 1996). They are also bitter, acrid, or astringent (Rousseff, 1990). Compliance with the recommended *Brassica*–rich diets by cancer patients may well be influenced by PROP taster status.

Whether PROP tasting also affects freely chosen diets in a community setting is a separate issue. For the most part, studies on PROP tasting and food preferences have made use of food preference checklists or self-reported frequencies of food use (Fischer et al., 1961; Glanville and Kaplan 1965; Drewnowski et al., 1999a, 2000; Mattes and Labov, 1989). There are virtually no data on PTC/PROP tasting and actual food consumption, measured using standard methods of dietary intake assessment. There are no published population-based studies on PROP tasting, diet structure, and the risk of chronic disease. Even so, researchers have proposed that PROP tasters consume less dietary sugar and fat than do nontasters, consume lower-fat diets and less dietary energy overall, and have lower body mass indices (BMI = kg/m^2) and lower plasma cholesterol levels (Duffy et al., 1999). Venturing into epidemiology, researchers suggested that PROP tasting may protect against obesity and lower the risk of coronary heart disease. There is no evidence at this time to support any such assertions. They are based on extrapolations of limited laboratory data to population-based research on diets and health.

The diet-mediated pathway between genetic taste markers and health parameters is outlined in Table 1. It combines laboratory-based studies on bitter taste with epidemiological research on diets and health. A convincing demonstration that genetic taste markers alter dietary exposure and, potentially, disease risk would have major implications for nutritional epidemiology and public health. However, two lines of evidence are required. First, we need to show that PROP tasters and nontasters differ not only in their food preferences but also in their patterns of food consumption. Self-reported food preferences are not always good proxy measures of actual intakes. Second, any taste-related changes in dietary exposure would have to be linked in a causal manner with health parameters and chronic disease risk. So far, few studies have assessed such a broad range of variables in the same subject population.

Assigning PROP taster status and linking PROP sensitivity to other bitter tastes is the domain of sensory studies. Tracking causal associations between genetic taste markers, food consumption patterns, and chronic disease risk is the domain of nutritional epidemiology. Laboratory studies are typically based on small samples of convenience, which are rarely stratified by race/ethnicity, gender, or age. Sensory data are commonly treated as continuous variables, with statistical tests based on analyses of

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Table 1 Measures of Taste Functioning, Food Preferences, and Diet and Health Parameters[a]

Type of data	Methods and procedures
PROP taster phenotype	Detection thresholds, intensity ratings, hedonic ratings
Bitter taste response	Intensity ratings, hedonic ratings, ranking
Sensory response	Intensity and hedonic ratings for sweet, salt, fat
Food preferences	Food preference checklists, frequencies of use
Dietary intake assessment	Food records, 24-hr food recalls, food frequency questionnaires
Biomarkers of exposure	Vitamin C, carotenoids
Biomarkers of disease risk	Cholesterol, triglycerides
Covariates	Race and ethnicity, age, education, income, marital status
Health parameters	BMI, body fat percentage, waist/hip ratio
Health outcomes	Disease risk (cancer, cardiovascular disease)

[a] PROP, 6-*n*-propylthiouracil; BMI, body mass index.

variance and tests of difference between the means. In contrast, epidemiological studies make extensive use of categorical variables and use regression models to adjust for unequal distribution of covariates. Any claims regarding the influence of taste factors on diets and health must be tested by more rigorous techniques of epidemiological analysis.

II. MEASURING 6-*n*-PROPYLTHIOURACIL SENSITIVITY

For a long time, laboratory studies on PTC/PROP have been dominated by the threshold detection method (Harris and Kalmus, 1949; Kalmus, 1958, 1971). Individual PROP sensitivity was determined by using a series of 15 PROP solutions, ranging in concentration from 0.001 mmol/L to 3.2 mmol/L PROP. Each participant was presented with two identical cups, one containing PROP and the other containing water, and was asked to judge which of the two samples was bitter (Bartoshuk, 1979, 1980, 1993; Drewnowski et al., 1997abc, 1998). Two consecutive correct answers at the same concentration led to presentation of the less concentrated PROP solution. Reversal points were defined as the concentration at which a series of correct responses turned to an incorrect response, or vice versa.

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Generally PTC/PROP detection thresholds are based on a mean of five reversal points.

The bimodal distribution of PROP thresholds was then used to categorize participants as either tasters or nontasters. PROP tasters were defined as having thresholds <0.1 mmol/L, whereas nontasters had thresholds >0.2 mmol/L. Cases with thresholds between 0.1 and .02 mmol/L were rejected as unclassifiable, since the two distributions are said to overlap in that range (Bartoshuk et al., 1994). Analyses of threshold distributions confirmed that they were consistent with a two-component model. In other words, PROP thresholds allowed for a clear segregation of tasters and nontasters but did not distinguish between medium and high responsiveness to PROP. Identification of the most highly PROP-sensitive individuals or "supertasters" was accordingly based on a ratio of perceived PROP bitterness to the perceived saltiness of NaCl solutions (Bartoshuk et al., 1994).

In our studies, participants also tasted and rated five solutions of 0.032, 0.1, 0.32, 1.0, and 3.2 mmol/L PROP as well as five solutions of NaCl. Following the earlier approach of Lawless (1979, 1980), PROP solutions were arranged around the antimode (0.1 mmol/L PROP). Bitterness of each stimulus was rated by nine-point category scales, on which 1 = "not at all bitter" and 9 = "extremely bitter" (Peryam and Pilgrim, 1957).

Data shown in Figure 1 are for a clinical sample of adult females. The women were recruited from the Breast Care Clinic at a large hospital center in the Midwest (Drewnowski et al., 1999; 2000). The sample included individuals newly diagnosed with breast cancer and cancer-free controls. The women were weighed and measured and completed taste tests, food preference checklists, food records and a food frequency questionnaire. They were classified as PROP tasters ($n = 265$) or nontasters ($n = 75$) on the basis of the distribution of PROP thresholds. Eighteen women were not classifiable by the threshold detection method.

The PROP detection thresholds were inversely correlated with summed bitterness intensity ratings for the five PROP solutions. Figure 1 also shows a significant difference in taste response profile for five PROP solutions by PROP taster status. As expected, increased perceived bitterness was associated with a greater dislike of PROP solutions.

Threshold-based procedures for assigning PROP taster status have some limitations. First, sensory acuity for very dilute solutions of PROP provides a limited picture of how bitterness response might influence individual food preferences and eating habits. Second, the ability to taste PROP is not an all-or-none phenomenon but a continuously distributed variable. Sensitivity to PROP is influenced, moreover, by race and eth-

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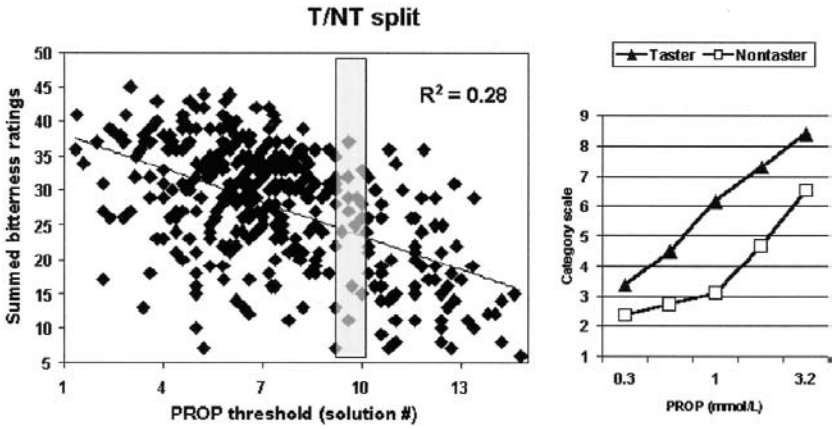

Figure 1 Left panel, relationship between PROP taste detection thresholds and summed bitterness intensity ratings for five PROP solutions. Data are for 265 PROP tasters, 75 nontasters, and 18 unclassified. Right panel, bitter taste responses to PROP solutions by PROP taster status. PROP, 6-*n*-propylthiouracil; T, taster; NT, nontaster.

nicity, gender, and age. Women are likely to be more PROP-sensitive than are men; Asians and Africans are more sensitive than are Caucasians (Parr, 1934; Guo et al., 1998); and children and young adults are more sensitive than are older adults (Drewnowski et al., 2000; Prutkin et al., 2000). Whether PROP sensitivity among women is modulated by hormones or declines after menopause remains unclear. As a genetic taste marker, PROP taster status is influenced by a surprisingly wide range of factors.

An alternative procedure to characterize PROP taste response using intensity scaling of PROP solutions is described fully elsewhere (Drewnowski, 2003). There has been disagreement as to which scaling methods best capture individual differences in taste response to PROP. The present analyses are based on the traditional threshold method, used in most past studies on PTC/PROP tasting and food aversions.

III. 6-*n*-PROPYLTHIOURACIL AND SENSORY RESPONSE

Threshold-derived PTC/PROP taster status has been linked with greater taste responsiveness to sodium and potassium benzoate, potassium chlo-

ride, caffeine, quinine, and saccharin, but not to urea (Bartoshuk et al., 1988, Gent and Bartoshuk, 1983; Hall et al., 1975). Those studies led to suggestions that PTC/PROP tasters would avoid both coffee and saccharin-sweetened soft drinks (Bartoshuk 1980). However, not all studies provided consistent results, and some of the observed differences, though significant, were minuscule. More recent studies confirmed that PROP tasters found caffeine more bitter (Ly and Drewnowski, 2001) and that aftertaste intensity for caffeine (0.018 mol/L) was higher among tasters than nontasters (Neely and Borg, 1999). Other studies went beyond the classic stimuli of taste psychophysics to show that PROP tasters were also more sensitive to naringin, a bioactive flavonoid in grapefruit juice, fermented soy products containing bitter isoflavones, and infusions of green tea containing catechins and epicatechins (Akella et al., 1997; Drewnowski et al., 1997b,c). However, although significant, the effects of PROP taster status on sensory response to bioactive phytochemicals were not particularly strong.

Another sensory study (Kaminski et al., 2000) did not demonstrate strong effects of PROP taster status on sensory preferences for instant coffee and steamed brussels sprouts presented in the laboratory. Reports that PROP tasting was associated with enhanced oral burn of capsaicin (Tepper and Nurse, 1997) suggested that PROP tasters would also avoid hot and spicy foods. Other reports suggested that PROP tasters were more likely to avoid alcoholic beverages (Pelchat and Danowski, 1992), though again not all studies produced consistent results (DiCarlo and Powers, 1998).

Low concentrations of sucrose, saccharin, and neohesperidin dihydrochalcone, an intense sweetener, tasted sweeter to PTC/PROP tasters than to nontasters (Gent and Bartoshuk, 1983). Duffy and associates (1996) reported that PROP supertasters were highly sensitive to the mouthfeel and texture of fats, provided in the form of a plain heavy cream. Elsewhere PROP-sensitive subjects gave higher fatness ratings to salad dressings (Tepper and Nurse, 1997). The PROP tasters were reported to dislike sweet sucrose solutions (Looy and Weingarten, 1992) and the oral sensation of emulsified fat (Duffy et al., 1999; Prutkin et al., 2000). Those data were interpreted to mean that PROP tasters also avoided sweet and high-fat foods and consumed a lower proportion of dietary fat and less dietary energy overall.

However, reports that PROP tasters were more sensitive to the sweet taste of solutions of sucrose, saccharin, and neohesperidin DC were not replicated in other studies. PROP tasting had no impact on sweetness

ratings or preferences for sucrose solutions or for a selection of sweetened dairy products differing in concentration of sugar and fat (Drewnowski et al., 1997a,c). Reports that PROP tasters showed a differential sensory perception of fat texture were not confirmed. Using 15 different sugar–fat mixtures of differing sugar and fat content, Drewnowski et al. (1998) found no differences in sweetness, creaminess, or overall acceptability ratings by PROP taster status in a sample of 118 young women. There is no convincing evidence at this point that PROP tasting is linked to a sensory dislike of sweet solutions or fat-containing foods.

The perception of bitter taste can be masked or modified through the presence of fat, sugar, or salt. Sweetening PROP solutions with neohesperidin DC reduced differences in perceived bitterness intensity and hedonic ratings between PROP tasters and nontasters (Ly and Drewnowski, 2001). Confirming prior data (Lawless, 1979), sweetener effects on bitterness intensity ratings were significant for tasters, but not for nontasters, whose ratings were already at the floor. These data are shown in Figure 2. That same study, conducted with 54 young women, revealed that sweetening caffeine solutions with neohesperidin DC completely eliminated differences in hedonic response between tasters and nontasters. In other

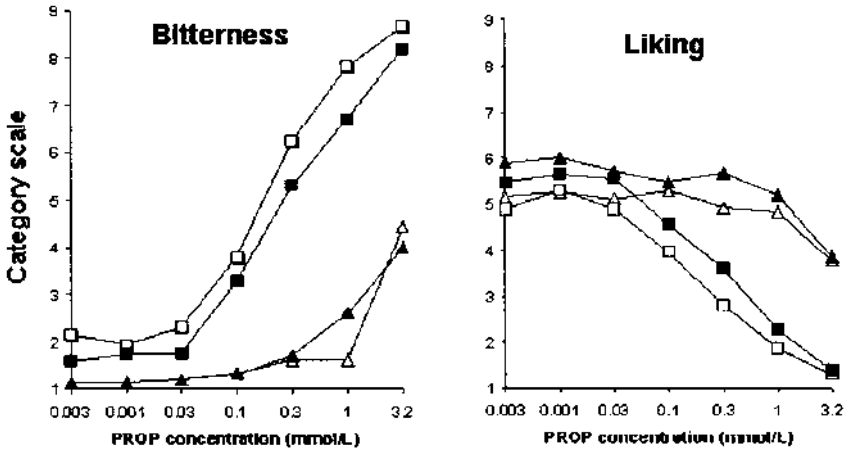

Figure 2 Bitterness intensity ratings and hedonic ratings by PROP taster status: left panel, bitterness intensity rating; right panel, hedonic rating. □, Tasters; Δ, nontasters. Data are for five PROP solutions (□, Δ) and for PROP solutions sweetened with neohesperidin DC (▲). PROP, 6-*n*-propylthiouracil.

words, the impact of genetic taste markers on preferences for caffeine was eliminated by the simple addition of a sweetener (Ly and Drewnowski, 2001). Along the same lines, there were no differences by PROP taster status in sensory preferences for white, milk, and dark chocolate (Ly and Drewnowski, 2001). Chocolate contains bitter polyphenols, in combination with both sugar and fat. Although PROP tasters and nontasters may differ sharply in their perception of some bitter compounds presented in aqueous solutions, such differences are minimized when the taste stimuli are real foods. Accordingly, the impact of PROP taster status on diet structure and eating habits would be expected to be modest, at best.

IV. 6-*n*-PROPYLTHIOURACIL AND FOOD PREFERENCES

Early studies, based on food preference checklists, showed that PTC/PROP tasters disliked cruciferous and green vegetables, rhubarb, sauerkraut, beer, coffee, and various sharp cheeses (Glanville and Kaplan, 1965; Forrai and Bankovi, 1984). However, the data were not always consistent, and other studies did not link PTC/PROP sensitivity with a robust pattern of food dislikes or food aversions (Mattes and Labov, 1984). Studies on the consumption of cruciferous vegetables by elderly women showed only modest effects of PROP sensitivity on food choices (Niewind et al., 1988). Low frequency of consumption may have been a problem, since vegetable consumption was low among tasters and nontasters alike.

A recent study (Drewnowski et al., 1999b), based on 159 young women, mean age 27.0 years, examined self-reported preferences for 171 foods on a food preference checklist. Participants indicated how much they liked or disliked each food item, using the 9-point hedonic preference scale. The PROP tasters reported lower preferences for coffee and espresso, but not for tea or iced tea. Respondents who expressed a decided dislike for coffee (ratings <3 on a 9-point scale) were, almost without exception, PROP tasters. In the same study, preferences for brussels sprouts, cabbage, and spinach were lower among PROP tasters than among nontasters (Drewnowski et al., 1999b). No other major differences in food preference were observed.

Another study examined self-reported food preferences by PROP taster status in a clinical sample of adult women (Drewnowski et al., 2000). The patients were tested before (or shortly after) diagnosis and before any

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surgical, chemotherapy, or nutritional intervention. All participants were given a 171-item food preference checklist that included foods from every food group and were asked to indicate how much they liked or disliked each food on a 9-point hedonic preference scale. The strongest effects were obtained for cruciferous vegetables and coffee. Participants who reported disliking cruciferous vegetables (rating <5) were, without exception, PROP tasters (Drewnowski et al., 2000). Preferences for most other foods, including fats and sweets, were not affected by PROP taster status.

The ability to taste PROP does not appear to be associated with a heightened response to many other bitter compounds present in everyday foods. Studies suggest that these compounds may represent different classes of bitter taste that may well correlate with each other, but not with PROP (Delwiche et al., 2002). Whereas the connection between PROP and caffeine is well established, the connection between PROP and phenolic compounds in vegetables and fruit is not. Studies have not demonstrated the impact of PROP sensitivity on the taste response to catechins, flavonoids, and condensed tannins (Noble, 1994). Even if PROP were linked to other bitter tastes, the bitterness of foods is readily modified through the addition of fat, sugar, or salt. As a result, genetic sensitivity need not predict avoidance, contrary to some past hypotheses.

V. 6-*n*-PROPYLTHIOURACIL AND FOOD CONSUMPTION

Reported links between PROP-tasting and a greater dislike for fat, sugar, salt, alcohol, and calories were, for the most part, contradicted or remain unconfirmed. Reports that PROP tasting is associated with lower energy intakes are contradicted by data presented in Table 2. The data are for a subset of the clinical sample of adult women for whom dietary intake data were available (Drewnowski et al., 1999b, 2000). These data are for 237 female PROP tasters and 63 nontasters. The data are based on a validated food frequency questionnaire developed by the Fred Hutchinson Cancer Research Center in Seattle. It can be seen that PROP tasters and nontasters had comparable intakes of energy and principal nutrients. There were no significant differences in the consumption of energy from carbohydrate or fat. Intakes of vitamin C, dietary fiber, and folate, adjusted for energy, are useful indices of fruit and vegetable consumption. As indicated later, no significant differences were observed between the two groups. There is no

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Table 2 Dietary Intake Data by 6-*n*-Propylthiouracil Taster Status[a]

Dietary data	Tasters, $n = 237$	Nontasters, $n = 63$	$P <$
Energy, kcal	1703 ± 28	1688 ± 60	NS
Fat, % energy	28.9 ± 0.5	29.0 ± 0.9	NS
Carbohydrate, % energy	55.6 ± 0.6	54.5 ± 1.1	NS
Protein, % energy	16.0 ± 0.2	17.1 ± 0.5	0.01
Alcohol, g	3.1 ± 0.4	3.1 ± 0.8	NS
Cholesterol, mg	234 ± 4	230 ± 7	NS
Calcium, mg	700 ± 19	659 ± 32	NS
Vitamin C, mg/1000 kcal	70 ± 3	79 ± 6	NS
Fiber, g/1000 kcal	9.7 ± 0.3	9.3 ± 0.5	NS
Folate, mg	231 ± 7	229 ± 14	NS

[a] Data are means and standard error of the mean (SEMs). Data are for a clinical sample of adult women.

Source: Drewnowski et al., 1999b, 2000.

evidence that PROP taster status has a major impact on energy intakes or diet structure.

VI. 6-*n*-PROPYLTHIOURACIL AND BODY WEIGHT

One persistent notion has been that PROP tasters eat less food and are therefore thinner than are nontasters (Tepper and Ullrich, 1999). Reports that some PROP tasters appeared to have lower body mass indices (BMI = kg/m^2) than did nontasters (Duffy et al., 1999) gave rise to suggestions that PROP tasting protects against obesity. However, those studies were limited to very small samples of college students. Epidemiological studies using regression models to account for unequal distribution of covariates have found no connection between PROP tasting and BMI (Drewnowski et al., 2001).

Data in Table 3 are for the same clinical sample of 340 adult women (Drewnowski et al., 1999, 2000). All patients were weighed and measured. Waist and hip circumferences were obtained with a tape measure, whereas fatfold thickness at multiple sites was measured with calipers by trained

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Table 3 Patient Data by 6-*n*-Propylthiouracil Taster Status[a]

Patient characteristic	Tasters, $n = 265$	Nontasters, $n = 75$	$P <$
Age, yr	49.2 ± 0.7	50.9 ± 1.3	0.05
Weight, kg	70.2 ± 0.9	73.0 ± 1.9	NS
Height, cm	164.4 ± 0.4	163.8 ± 0.7	NS
BMI, kg/m^2	26.0 ± 0.3	27.3 ± 0.7	NS
Waist circumference, cm	32.5 ± 0.3	33.9 ± 0.7	NS
Hips circumference, cm	41.3 ± 0.3	42.0 ± 0.6	NS
Waist/hips ratio	0.78 ± 0.01	0.80 ± 0.01	NS
Triceps skinfold, mm	28.1 ± 0.5	30.0 ± 1.0	NS
Thigh skinfold, mm	36.6 ± 0.7	37.6 ± 1.4	NS
Suprailiac skinfold, mm	30.8 ± 0.7	34.2 ± 1.9	NS
Sum of skinfolds, mm	95.5 ± 1.7	101.5 ± 3.3	NS

[a] Data are means and standard error of the mean (SEMs). Data are for a clinical sample of adult women. BMI, body mass index.
Source: Drewnowski et al., 1999b, 2000.

staff. Fatfold thickness was used to calculate percentage of body fat. The PROP tasters were somewhat younger than nontasters, a finding consistent with past results (Drewnowski et al., 2001). Otherwise, tasters and nontasters did not differ on any other anthropometric measure.

Partial correlations (adjusting for age) showed the expected association between BMI and percentage body fat ($r = 0.67$; $p < 0.01$) and between BMI and the waist/hip ratio ($r = 0.43$; $p < 0.01$). In contrast, partial correlation coefficients between PROP thresholds and BMI ($r = 0.03$; NS), percentage body fat ($r = 0.05$; NS), and waist/hip ratio ($r = 0.05$; NS) were not significant. A scatterplot of BMI values plotted against PROP thresholds is shown in Figure 3. Participants were then divided into those who were obese (BMI > 30) and those who were not. There was no relation between PROP taster status and obesity, as tested by using joint contingency tables followed by chi-square tests. A regression model did not link BMI with PROP taster status. A Pearson correlation linking PROP thresholds with body mass indices is largely meaningless, given that BMI is influenced by age, gender, race and ethnicity, physical activity level, education, occupation, and income.

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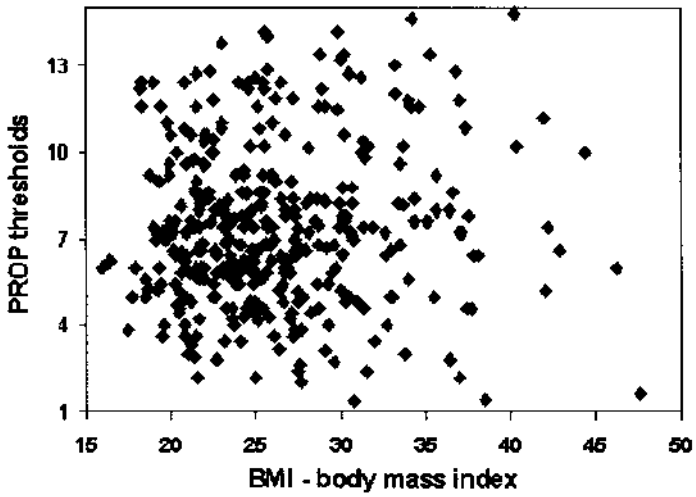

Figure 3 A scatterplot showing no relationship between PROP thresholds and body mass index (BMI = kg/m^2) values for a clinical sample of 358 adult women. Included are 265 PROP tasters, 75 nontasters, and 18 unclassified. PROP, 6-*n*-propylthiouracil.

VII. CONCLUSION

Self-reported acceptance ratings for a narrow range of bitter foods were influenced by PROP taster status. In particular, female PROP tasters tended to dislike black coffee, green tea, *Brassica* vegetables, and some salad greens to a greater extent than did nontasters. That result would suggest a degree of correlation between PROP sensitivity and responsiveness to caffeine, catechin, and glucosinolates in plant foods. The PROP tasters were also more likely to add sugar or cream to their coffee. No other major differences in reported food preferences were obtained between the two groups. The PROP taster status had no measurable impact on energy intakes, food choices, or eating habits in a clinical sample of adult women, as measured by rigorous techniques of dietary intake assessment. Body mass indices and body fatness were not affected by PROP taster status. The impact of taste genetics on food consumption is extremely modest and is likely to be tempered by cultural, social, and behavioral factors. The likely answer to whether PROP tasting affects disease risk through a diet-mediated mechanism is no.

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10

Genetic Variation in Taste
Potential Biomarker for Cardiovascular Disease Risk?

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I. INTRODUCTION

Cardiovascular disease (CVD) is the leading cause of death in the United States and other developed countries. This disease group includes coronary heart disease (CHD), hypertensive disease, rheumatic heart disease, and stroke. Primary prevention for CVD aims to modify the risk factors or prevent the progression of these risk factors into new-onset disease. The quality of the diet plays a major role in the promotion of health and prevention of chronic disease (1). Dietary behavior can modify the risks for CVD including dyslipidemia, hypertension, and obesity (2). The recommendations for preventing CHD also focus on eating patterns that limit total fat, alcohol, and salt intake; maintain healthy body weight; and increase fruit and vegetable intake (3).

Effective intervention programs must guide individuals to make appropriate food choices in order to improve the quality of the diet and

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reduce CVD risk. The taste of foods is an important reason why consumers choose to eat what they do (4). Taste used in this way extends beyond the strict definition of true taste or the perception of salt, sweet, sour, and bitter to include olfactory components and oral somatosensatory (e.g., tactile, temperature, irritant) qualities of food flavor. Taste and some oral somatosensory experiences from foods and beverages are not perceived equally in all individuals. One source of variation in perception is genetic. This genetic variation may influence consumer behavior toward foods and beverages and ultimately link to risk of chronic diseases such as CVD.

A framework for investigating the influence of genetic variation in taste on CVD risk is shown in Fig. 1. Humans experience oral sensations from foods and beverages differently because of genetic variation in taste. Differences in oral sensations influence our liking/disliking for foods and beverages, and, because we tend to eat what we like and avoid what we do not like, our dietary intake and ultimately CVD risk. This chapter reviews the characterization of genetic variation in taste and provides data to support associations between taste genetics and (a) oral sensations from

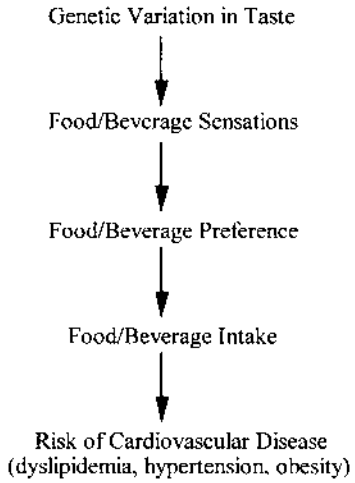

Figure 1 Framework for investigating associations between genetic variation in taste and risk of cardiovascular disease through dietary behavior.

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fat, alcohol, and sodium chloride; (b) preference for and intake of high-fat foods and alcoholic beverages; and (c) body composition and serum lipids.

The Taste Genetic and Dietary Behavior Study in the School of Allied Health at the University of Connecticut is a source of some data presented in this chapter. This ongoing observational study is designed to examine the relationship between genetic variation in taste and food/beverage sensations, dietary behavior, and nutritional status in adults. A complete description of the subject recruitment and inclusion criteria has been published (5). Here we report on 75 subjects who were primarily Caucasian (range 20 to 39 years), stated that they had good health, and denied smoking cigarettes or having a high level of dietary restraint [Assessed with the Concern for Dieting subscale of the Restrained Eating Scale (6,7) and the Three Factor Eating Questionnaire (8)]. The subjects were recruited to represent variability in perceived bitterness of 6-*n*-propylthiouracil (PROP) in both men and women but not to have a significant history of taste-related disorders including middle ear infections and head trauma. These pathological conditions confound taste genetic classification (9) and thus the ability to examine genetic links to dietary behavior.

Subjects traveled to the laboratory for three separate visits (usually 1 wk apart) to assess oral sensations, food and beverage preferences, dietary intake, body composition, PROP tasting, and fungiform papilla density as well as to provide blood samples for serum lipid analysis and taste gene analyses. For PROP tasting, subjects rated the intensity of 1/4 log concentrations of NaCl (0.01M to 1.0M, presented in random order and in duplicate) and then PROP (0.032mM to 3.2 mM, presented in random order and in duplicate) on the general Labeled Magnitude Scale (gLMS) (10,11). Concentrated PROP was given last at the end of the third session to prevent potential context effects on intensity ratings of other stimuli (12). The number of fungiform papillae at the tongue tip was determined with videomicroscopy using the method of Miller and Reedy (13). For this procedure, the subject's tongue was painted with blue food coloring to contrast between stained filiform and unstained fungiform papillae. Subjects reclined and steadied their stained tongue between two plastic slides attached with screws. Magnification (15 times) clearly distinguished fungiform from filiform papillae. The images are recorded for 3 to 5 min to allow subsequent counting of the fungiform papillae number in a 6-mm-diameter circle on right and left tongue tips.

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II. CHARACTERIZING GENETIC VARIATION IN TASTE FOR DIETARY BEHAVIOR AND "CARDIOVASCULAR DISEASE" RISK STUDIES

A. Bitterness of 6-*n*-Propylthiouracil

Humans show genetic variation in the ability to taste the bitterness of phenythiocarbamide (PTC) and PROP, two compounds containing the N-C=S group. The discovery that some individuals are blind to PTC bitterness was accidental (14). Initial work in PTC/PROP tasting classified individuals into two groups with detection thresholds (15): nontasters, those thought to be homozygous recessive, and tasters, those thought to be either heterozygous or homozygous dominant for the taster gene. Thresholds do not predict perceived intensities of more intense stimuli and thus may have limited utility for understanding of sensory influences on dietary behavior. An example of disconnection between threshold and intensity for

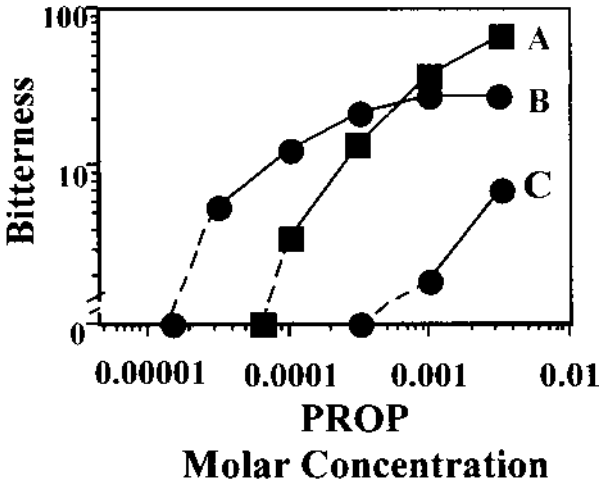

Figure 2 Threshold and psychophysical functions are shown for three individuals: A, B, and C. Perceived bitterness was determined with the gLMS. Individual B has the lowest PROP threshold, but bitterness grows more slowly with concentration than for individual A; individual C has an elevated threshold and experiences less bitterness at all suprathreshold concentrations. Thus, threshold may not correctly characterize the perception of concentrated oral sensations. gLMS, general Labeled Magnitude Scale; PROP, 6-*n*-propylthiouracil.

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PROP bitterness is illustrated in Fig. 2. Individual B has the lowest PROP threshold, but bitterness grows more slowly with concentration than it does for individual A. Individual C has an elevated PROP threshold and experiences less bitterness at suprathreshold concentrations than individuals A and B. The data presented in this chapter support characterizing of individuals by the top of their psychophysical function (0.0032M PROP) to identify those who live in the most diverse oral sensory worlds and who differ most in their food behavior.

Studies from our laboratory have relied on characterizing variation in PROP tasting by using perceived intensity measures. The experiments described later either scale the bitterness of PROP with magnitude estimation normalized to a nonoral standard (see Chapter 1 in this volume) or with the gLMS (10,11). These scaling techniques permit valid comparisons of perceived intensity across groups (see Chapter 1 in this volume). A number of papers describe three groups of tasters (i.e., nontasters, medium tasters, and supertasters); however, the psychophysical functions claimed to represent medium tasters are barely distinguishable from those for supertasters (16,17). Not surprisingly, these papers fail to discern sensory and nutrition differences across the PROP taster groups. In reality, medium tasters and supertasters show considerable variation in the perceived bitterness of PROP.

Figure 3 shows data from the Taste Genetic and Dietary Behavior Study of 75 subjects who were recruited for diversity in PROP tasting. The functions, produced with the gLMS, demonstrate a clear separation of the three taster groups. These subjects also produce the usual bimodal distribution of PROP threshold.

B. Fungiform Papillae

Humans show variation in the density of fungiform papillae on the anterior tongue. The genetic control of fungiform papillae is not clear, although there are genetic links to development through brain-derived neurotrophic factor (18) as well as to the expression of sensory and autonomic disorders in which individuals do not have the papillae [e.g., familial dysautonomia (19)].

Those with the highest density of fungiform papillae tend to experience the most intense sensations from taste as well as oral somatosensory stimuli. Taste intensity (20) and threshold (21) are related, within limits, to the area of the tongue stimulated. Miller and Reedy (22) first suggested an association between number of fungiform papillae taste buds (indicated by taste pores) and bitterness of PROP. In collaboration with Miller (23), we

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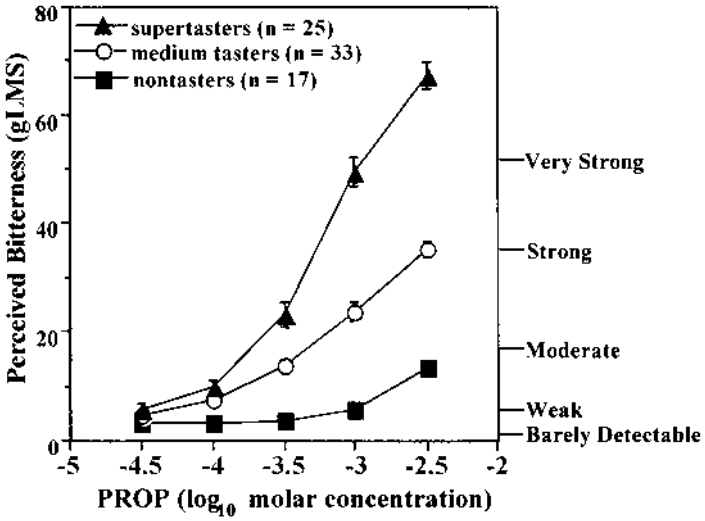

Figure 3 Perceived bitterness rated on the gLMS by PROP concentration in 75 subjects from the Taste Genetic and Dietary Behavior Study. Subjects are divided into three groups for the purpose of showing separation in functions between nontasters (those tasting PROP as less than "moderate"), medium tasters (those tasting PROP between "moderate" and "very strong"), and supertasters (those tasting PROP greater than "very strong"). gLMS, general Labeled Magnitude Scale; PROP, 6-*n*-propylthiouracil.

showed that PROP supertasters had, on average, the greatest number of fungiform papillae and taste buds. The relationship between PROP tasting and fungiform papillae density has also been reported by Tepper and Nurse (24), Yackinous and Guinard (16), and Chopra and colleagues (25). In 75 subjects studied in the Taste Genetic and Dietary Behavior Study, the correlation between fungiform papillae density and bitterness of 0.0032M PROP is significant ($r = 0.42$, $p < 0.0001$) and strongest in females ($r = 0.51$, $p < 0.001$). Those who taste PROP as intensely bitter (i.e., supertasters) may have more PROP receptors per fungiform papilla as well as a greater density of fungiform papillae (26).

Fungiform papillae (anterior tongue) hold taste buds and receive innervation from taste [chorda tympani nerve (CN VII)] and somatosensory [trigeminal nerve (CN V)] nerve fibers (27,28). Chorda tympani nerve fibers synapse with cells in taste buds. Some trigeminal nerve fibers

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surround taste buds without synaptic contact (27,28); these are thought to be primarily nociceptive (28,29). Some trigeminal nerve fibers going to other locations in the fungiform papillae appear to mediate touch (30–32).

Our understanding about the relationships between fungiform papillae and oral sensations, including the bitterness of PROP, is limited by the effects of the environment (e.g., pathological conditions) as well as maturation (e.g., changes in sex hormone levels). Taste may be damaged without affecting the fungiform papillae. These papillae are formed early in gestation (33) and remain intact unless the trigeminal nerve is damaged (34–36). Thus an individual who has a taste-related abnormality may exhibit low bitterness (37) or elevated oral somatosensation (38) in relation to number of fungiform papillae.

Oral sensation also appears to be influenced by sex hormones. The distribution of PROP/PTC tasting differs in males and females; the female distribution is skewed toward higher bitterness (23). Females have a higher average taste bud density on the anterior tongue than do males ($p < 0.05$), and females are skewed to the top of the distribution for density of fungiform papillae and taste buds ($\chi^2 = 8.627$, $p < 0.01$, $n = 100$) (23). This finding has been confirmed in a separate sample, in which up to 17% of the females had higher density of fungiform papillae and taste pores than males (34). Females also have greater variability in PROP bitterness than do males, even when this variation is anchored to the number of fungiform papillae (34). Because of the recruitment strategy, females and males did not differ significantly in PROP bitterness in the Taste Genetics and Dietary Behavior Study. However, females were skewed to higher density of fungiform papillae than males ($\chi^2 = 5.483$, $p < 0.02$, $n = 75$).

Variations in taste perception and oral somatosensation are also seen across changes in sex hormone status (see Ref. 34 for a review). Women of childbearing age show greater variation in taste and oral sensation than do men. Taste varies across menstruation (39). Bitterness of quinine hydrochloride (QHCl) (40) and of PTC (41) increase during the first trimester of pregnancy. Enhanced ability to taste bitter may continue past pregnancy: Romanus (42) reports that women who have had children are less likely to be nontasters than women who have not. During menopause, bitter perception appears susceptible to age-associated changes (43). There appear to be fewer PROP supertasters in older than in younger women (44–46); data supporting this finding (44) are discussed later.

Studying relationships between oral sensation and dietary behavior requires consideration of the complex interactions among genetics, pathological conditions, and sex on oral sensation. Study designs that exclude

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individuals who report a significant history of taste-related pathologies (e.g., head trauma and otitis media) may increase the ability to examine genetic influences on oral sensations and dietary behavior. Aging increases chance of exposure to these pathological conditions as well as to medications that alter oral sensations, thus complicating the investigation of taste genetics and diet relationships. Examining taste genetic and diet relationships in females or males separately or using sex and taste genetics as independent variables to predict dietary behavior can account for sex influences (i.e., biological) on oral sensation as well as combined sex and gender influences (i.e., biological and sociocultural) on dietary behavior.

6-*n*-Propylthiouracil bitterness and fungiform papillae density can also serve as separate contributors to the prediction of dietary behavior (47) and may increase our understanding of complex interactions among genetics, pathological conditions, and sex on oral sensations. Fungiform papillae density may provide a stable measure of genetic endowment but does not appear to reflect environmental and maturational influences on oral sensation. Bitterness of PROP reflects genetic, environmental, and maturational influences. We have experimented with using both measures together to define groups likely to experience the most divergent oral sensations. Individuals who taste PROP as strongly bitter and have an elevated number of fungiform papillae may have different oral sensory worlds and dietary behaviors than those who test low on both measures or those for whom the two measures are discordant. Preliminary data show that separating individuals by using both measures showed the strongest relationship to serum lipids (see later discussion).

III. GENETIC VARIATION IN TASTE AND ORAL SENSATIONS FROM FAT, ALCOHOL, AND SALT

A. Fat

In 1996 we presented data at the Association for Chemoreception Sciences (AChemS) meeting on associations between PROP bitterness and the creaminess of high-fat milk products (48). In this study, 69 adults (mean age 25 $\pm$ 8 standard deviation (SD); range 17 to 40 years) provided creaminess ratings of skim milk ($<$ 0.5% fat), 1% low-fat milk, 2% low-fat milk, whole milk (3.5% fat), half and half (11.5% fat), heavy cream (36% fat), and heavy cream plus oil (54% fat), which were served cold. For the procedure, subjects first provided magnitude estimates of five NaCl solutions (1/4 log steps from 0.01M to 1.0M), always starting first with the

0.1M NaCl. The milk product series was then presented in random order and repeated. Subjects were instructed to use the same intensity scale for the saltiness of NaCl and the creaminess of the milk products. To permit comparisons among subjects (49), the magnitude estimates of the creamy ratings were normalized. For this normalization, the geometric mean of the 0.32M and 1.0M NaCl was first calculated. Normalized creaminess ratings were obtained by multiplying the subject's normalization factor (average of the geometric means divided by the individual's geometric mean) by the creaminess ratings.

For PROP scaling, subjects provided magnitude estimates of five concentrations of NaCl (1/4 log steps from 0.01M to 1.0M) and then PROP (1/4 log steps from 0.000032M to 0.0032M). The stimuli were randomized within a series and the order of presentation aimed to minimize context effects (50). A ratio of the intensity of PROP to NaCl (as described in Ref. 23) was used to compare the ratings of creaminess. Figure 4 shows significant associations between PROP ratio and the perceived creaminess of heavy cream with oil, heavy cream, and whole milk. As expected, the association between PROP ratio and creaminess of skim milk was not significant. Use of NaCl to normalize both the PROP and milk products may have underestimated the PROP effects as NaCl saltiness associates with PROP bitterness (see later discussion).

6-*n*-Propylthiouracil bitterness has also been shown to correlate with the oiliness of salad dressings (24) and corn oil (51) as well as the viscous sensations from a nonfat tactile stimulus, guar gum (51). Data from Prutkin and associates (51) suggest that the higher the density of fungiform

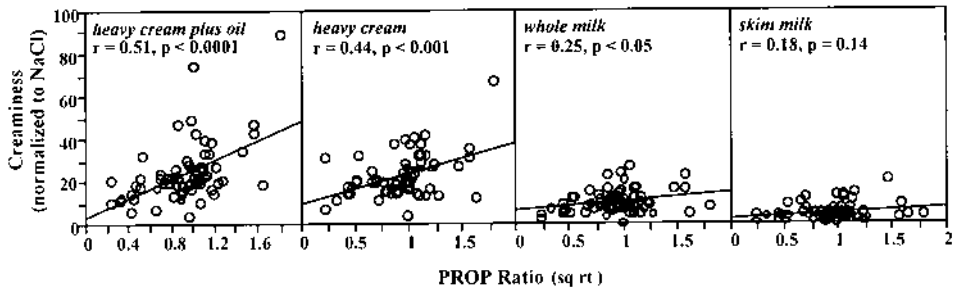

Figure 4 PROP bitterness presented as the PROP ratio (23) by the creaminess of milk products that vary in percentage fat (weight/weight) from 54% (heavy cream plus oil) to $<0.5\%$ fat (skim milk). PROP, 6-*n*-propylthiouracil.

papillae, the greater the tactile sensitivity according to two-point thresholds. More recently, Chopra and coworkers (25) report that those who taste PROP as more bitter and have more fungiform papillae also have greater spatial acuity as tested by letter recognition on the tongue tip.

Data from the Taste Genetics and Dietary Behavior Study show that the creaminess of heavy cream associates significantly with 0.0032M PROP bitterness and the density of fungiform papillae (Fig. 5). In this protocol, 75 subjects sampled heavy cream and eight high-fat foods (extrasharp cheddar cheese, very-low-sodium cheddar cheese, cream cheese, mayonnaise, milk chocolate, bittersweet chocolate, potato chips, low-sodium potato chips) and provided ratings of sweetness, saltiness, sourness, bitterness, creaminess/oiliness, as well as degree of liking/disliking on the gLMS.

The bitterness of PROP showed a significant association with overall creaminess/oiliness of the sampled high-fat foods (Fig. 6). In multiple regression with PROP and sex as independent variables, only PROP bitterness was a significant predictor of creaminess/oiliness of these sampled foods.

A number of studies have not to identified PROP effects on the oral sensations from fat in fat–sugar mixtures (52) as well as more complex mixtures (16). These findings are difficult to interpret as the sensations from the fat and PROP bitterness were measured with category scales that

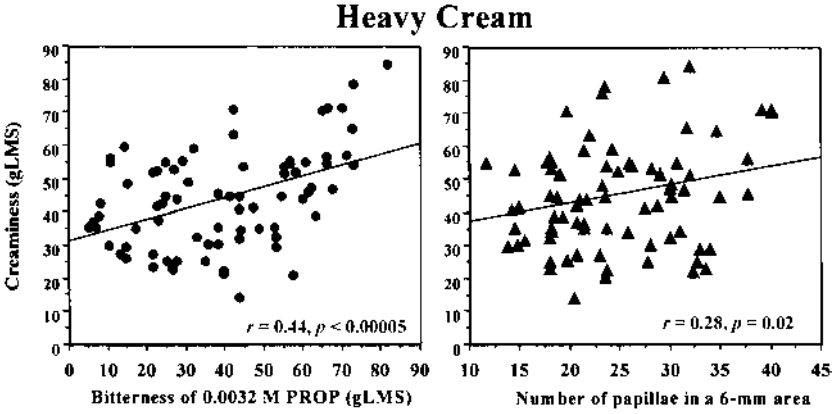

Figure 5 Perceived creaminess of heavy cream by bitterness of PROP (left) and number of fungiform papillae (right) in subjects in the Taste Genetic and Dietary Behavior Study.

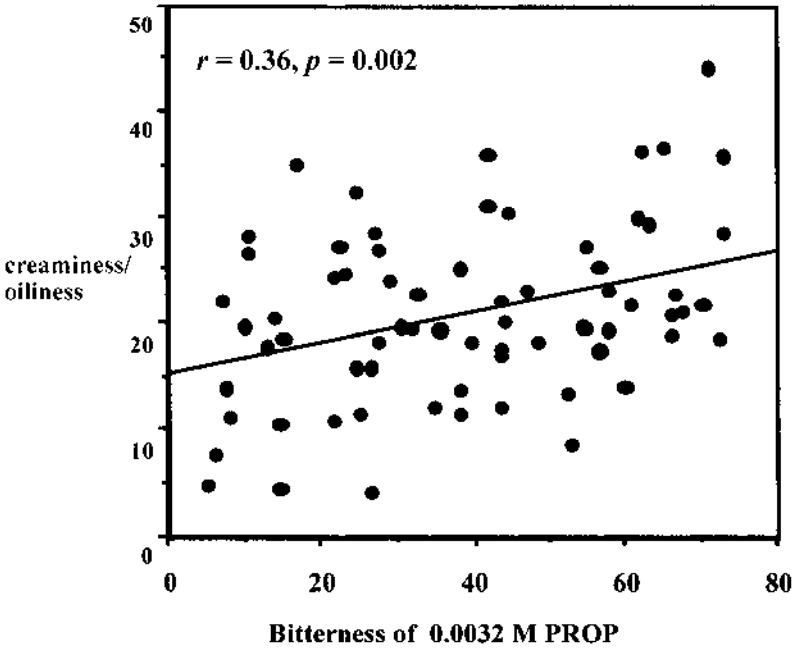

Figure 6 The creaminess/oiliness of a group of eight sampled high-fat foods by the bitterness of 0.0032M PROP in subjects in the Taste Genetic and Dietary Behavior Study. Sensory ratings were made on the gLMS. PROP, 6-*n*-propylthiouracil; gLMS, general Labeled Magnitude Scale. (From Refs. 10 and 11.)

cannot be used to make valid comparisons across groups (see Chapter 1 in this text). The Yackinous and Guinard study (16) also presented samples that did not differ in perceived fattiness ratings.

B. Alcohol Sensation

6-*n*-Propylthiouracil bitterness associates with alcohol bitterness and irritation/burn. In an early study, Bartoshuk and colleagues (53) categorized adults as nontasters, medium tasters, and supertasters on the basis of PROP thresholds and ratios to examine differences in bitterness and irritation from 10% ethanol applied to the tongue tip and 10% to 50% ethanol sampled with the whole mouth. All sensory ratings were measured

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with magnitude estimation and normalized to the saltiness of NaCl. For the 10% alcohol, supertasters tasted the bitterness more than medium tasters and medium tasters more than nontasters. The alcohol probe was perceived as more irritating to the supertaster than to either the medium tasters or the nontaster. For the whole mouth alcohol stimulus, supertasters and medium tasters perceived significantly more bitterness than the nontaster. The use of NaCl to normalize PROP and alcohol ratings may have underestimated the size of the PROP effects, as NaCl is saltier to those who taste PROP as more bitter (see later discussion). Data from the Taste Genetic and Dietary Behavior Study show a significant relationship between PROP bitterness and the intensity of 50% ethanol applied to the left tongue tip (5).

An association between PROP tasting and alcohol sensation was also shown by Prescott and Swain-Campbell (54), who reported that ethanol was more irritating to PROP tasters than to nontasters, and by Intranuovo and Powers (55), who found that some beer varieties are more bitter to those who taste PROP as very strongly bitter.

C. Sodium Chloride

At the 1997 Olfaction and Taste XIII: An International Symposium, Bartoshuk and colleagues (56) presented the finding that supertasters tasted NaCl as more salty than nontasters. In this study, PROP bitterness, NaCl saltiness, and tone intensity were measured with magnitude estimation. Using magnitude matching of Marks and Stevens (49,57), the perceived intensity of the tastants was standardized to the loudness of tones; this revealed that PROP bitterness associated with NaCl saltiness. Ko and associates (58) and Chapo and coworkers (59) also found PROP effects on NaCl saltiness by using the gLMS. In the former study, PROP bitterness associated significantly with the saltiness of 1.0M NaCl in solution as of 0.63M and 1.12M NaCl in chicken broth (59).

In contrast, some studies do not report PROP effects on NaCl saltiness. For example, Yackinous and Guinard (16) show functions for PROP and NaCl in nontasters, tasters, and supertasters. The psychophysical functions for NaCl saltiness in the nontasters exceeded those for the supertasters (see Chapter 1 in this volume for a description of a reversal of the PROP effect). They also tested PROP effects on saltiness in food systems in which the salt taste may have been masked (e.g., mashed potatoes, sour cream potato chips).

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IV. GENETIC VARIATION IN TASTE AND PREFERENCE FOR HIGH-FAT FOODS, ALCOHOLIC BEVERAGES, AND SALTINESS

A. Fat

On the basis of hedonic responses reported via questionnaire, we reported significant negative associations between PROP bitterness as well as fungiform papillae density and the degree of liking/disliking of 12 high-fat foods (cheeses, salty meats, salty snacks, added fat, whole milk); the association differed by sex (47). In females, those who tasted PROP as more bitter reported less acceptance for these high-fat foods than those who tasted PROP as less bitter ($r = -0.59, p = 0.005$). Males did not show this response.

Findings reported by Tepper and Nurse (60) support PROP effects on fat preference. Nontasters liked sampled high-fat salad dressing more than medium or supertasters. However, Yackinous and Guinard (16) reported a lack of association between PROP tasting and preference ratings for sampled foods including potato chips, chocolate drinks, mashed potatoes, and vanilla pudding. Because both studies used nine-point hedonic category scales, questions of validity similar to those raised by nine-point sensory scale arise. We created a hedonic gLMS from the original LMS by anchoring the ends with "strongest imaginable like/dislike" (neutral was the center) and looked at preference for sweetness (61) and fat (44). Schutz and Cardello (62) produced a hedonic scale for foods based on methods described by Green and colleagues (63,64), that is, similar to our hedonic gLMS. Both studies support the argument that hedonic experiences are intensitive and can be measured just as sensory experiences can.

In the Taste Genetics and Dietary Behavior Study, we examined PROP effects on preference for high-fat foods sampled by using our hedonic gLMS (65) and explored sex and creamy influences on preference for these foods. Subjects sampled bite-sized pieces of potato chips (regular, low-sodium), chocolates (milk and bittersweet), cheeses (extrasharp cheddar, low-sodium cheddar), cream cheese, and mayonnaise. In females, lower PROP bitterness associated with higher preference for high-fat foods; males showed the opposite response. The PROP and sex interactions on preference ratings from sampled foods (65) were consistent with questionnaire ratings (47).

Multiple regression analyses allowed us to examine interactions among PROP, sex, and creaminess on the preference for high-fat foods.

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The general assumption is that creaminess is a preferred food attribute (i.e., the creamier the better). Is this general assumption different for a female who tastes PROP as more bitter? In standard multiple regression, PROP, sex, and creaminess ratings each contributed significantly to predicting preference across a group of eight high-fat foods (see Sec. III.A), with a multiple $r = 0.46, p = 0.002$ (Table 1). Men, those who tasted PROP as less bitter, and those who reported more creaminess/oiliness assigned the highest preference ratings for the high-fat foods. There appears to be a group of females who taste PROP as intensely bitter and for whom the creaminess/oily sensations from high-fat foods are less pleasant. If examining each sex separately, PROP bitterness and degree of creamy/oily sensations are independent predictors of preference in females, whereas only the degree of creamy/oily sensations is a significant predictor in males.

The reasons for the interactions between creamy/oily sensations and PROP bitterness on preference for high-fat foods in females are not entirely clear. It may be that the supertaster female experiences a different array of sensory experiences from high-fat foods, and these experiences are less pleasant. These sensory experiences could relate to the density of fungiform papillae. Females in the present sample are skewed toward the highest density of fungiform papillae. This skew has been shown previously (34); approximately 10% of female supertasters have the highest density of fungiform papillae. Interestingly, Keller and coworkers (66) report a sex difference in fat preference in preschool children. Nontaster girls had higher preferences for high-fat dairy products than taster girls; no effects were seen in boys.

B. Alcohol

Higher PROP bitterness ratings associate with less liking for alcoholic beverages, presumably because of more intensely perceived bitter and irritation sensations. The preference for alcoholic beverages is negatively

Table 1 Multiple Regression Variables to Predict Average Preference Ratings for a Group of Eight High-Fat Foods

Variable	Partial cor.	*R*-square	*t*(62)	*p* Level
Sex (1 = female; 2 = male)	0.25	0.04	2.05	0.05
0.0032 PROP bitterness	−0.35	0.08	−2.80	0.007
Creaminess/Oiliness Ratings	0.33	0.08	2.77	0.007

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associated with the perceived bitterness of the alcoholic beverage (55) as well as the perceived intensity of an alcohol probe (5). In the latter study (Taste Genetic and Dietary Behavior Study), 75 subjects rated the degree of liking/disliking of a 50% ethanol probe applied to the left tongue tip. Could alcohol present enough of a noxious experience to a PROP supertaster to act as a sensory hindrance to drinking alcohol? Perhaps higher PROP perception may decrease the risk of overconsumption of alcohol and hence alcoholism.

C. Sodium Chloride

Individuals who taste PROP as more bitter report greater intensity from 1.0 MNaCl in solution and 0.63M and 1.12M in chicken broth as well as greater aversion for the 1.12M NaCl in chicken broth (59). High NaCl can stimulate taste sensations as well as oral irritation (67). Perceiving more irritation from NaCl may act as a sensory hindrance to overconsumption (68).

V. GENETIC VARIATION IN TASTE AND INTAKE OF HIGH-FAT FOODS, ALCOHOLIC BEVERAGES, AND SALT

A. Fat

Preliminarily, we reported a negative association between PROP bitterness and intake of high-fat foods (69). Unfortunately, PROP bitterness was scaled with the original Labeled Magnitude Scale [direction that the top of the scale was ''strongest imaginable oral sensation'' (63,64)], which incorrectly assumed that ''strongest imaginable oral sensation'' was equal across the continuum of PROP tasting. This assumption would have blurred distinctions between medium and supertasters; this finding has now been confirmed by using the gLMS for measuring the perceived bitterness of PROP (see later discussion).

Data from the Taste Genetics and Dietary Behavior Study also support associations between measures of taste genetics and frequency of high-fat food consumption (65). In this study, subjects reported their frequency of consuming high-fat foods on the Block Food Frequency Questionnaire (70) version 98.1 (see www.nutritionquest.com/validation.html for validation of this instrument). To increase the accuracy of

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this instrument, a registered dietitian interviewed each subject and coded the response for frequency and quantity of each food/beverage consumed, using pictures of serving sizes. Responses to the food frequency instrument allow ranking of subjects according to individual as well as groups of foods/beverages consumed (71). The risk of underreporting food intake was reduced with the exclusion of individuals with high dietary restraint (including weight loss dieting) (71,72). Within the study protocol, subjects also completed five nonconsecutive 24-hour food records. Measures of taste genetics associated significantly with neither total energy intake nor total energy intake expressed per kilogram body weight.

Forty of the foods from the frequency questionnaire could be considered high in fat (≥30% of energy from fat) including meats, eggs, cheeses, desserts, and condiments. The PROP bitterness valve and fungiform papillae number showed a negative correlation with yearly intake of the sum of these high-fat foods that was not significant in the entire sample but showed a trend toward significance in females ($p = 0.1$). Subgroups of high-fat foods can be made from these 40 foods by using either statistical or conceptual groupings. Statistical grouping is somewhat problematic when using parametric statistics such as principal component analysis, as the food frequency data are not normally distributed in this relatively small sample size of 75 subjects and previous attempts have proved unsuccessful at explaining sufficient variability with the factors created (73). Conceptual grouping may produce food groups that are not statistically reliable (i.e., low Cronbach's alpha); therefore, associating this group with another variable is problematic (73).

We took a novel approach to grouping foods on the basis of the direction of the relationship between the frequency of consuming the food and the measures of genetic variation in taste (65). 6-*n*-Propylthiouracil bitterness showed a negative association with intake of 25 of these 40 high-fat foods; these foods formed a statistically cohesive group (Cronbach's alpha = 0.78). Subjects who tasted little bitterness from the PROP reported consuming this high-fat food group significantly more frequently. 6-*n*-Propylthiouracil bitterness, body mass index (BMI: weight in kilograms divided by height in meters squared), and sex were entered into standard multiple regression analyses to predict frequency of consumption of the high-fat food group. In these analyses, sex was a significant contributor to the frequency with which high-fat foods were consumed and PROP was nearly significant (see Fig. 7).

Subsequent data analyses (65) show that the number of fungiform papillae on the anterior tongue also associates inversely with the frequency

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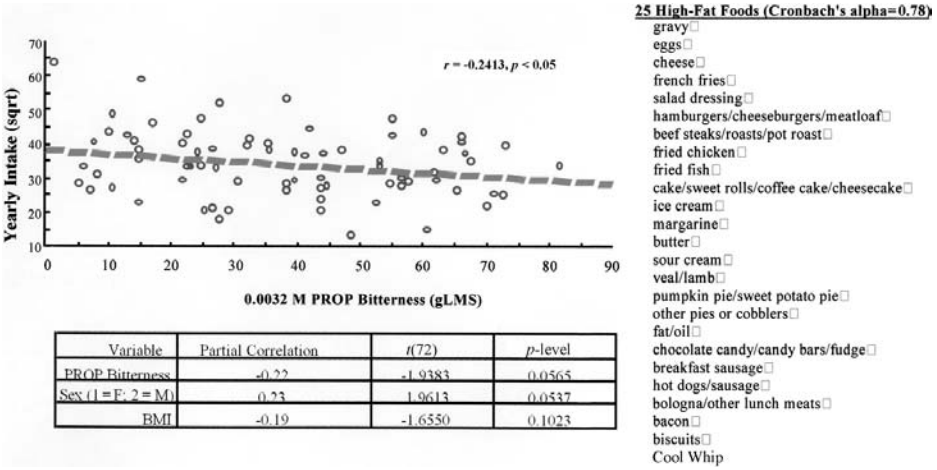

Variable	Partial Correlation	$t(72)$	p-level
PROP Bitterness	+0.22	-1.9383	0.0565
Sex (1 = F; 2 = M)	0.23	1.9613	0.0537
BMI	-0.19	-1.6550	0.1023

Figure 7 The graph shows yearly intake of high-fat foods (listed to the right) by the bitterness of 0.0032M PROP rated on the gLMS. In multiple regression, sex was a significant predictor of intake of these foods; PROP bitterness just missed significance ($p = 0.06$). PROP, 6-*n*-propylthiouracil; gLMS, general Labeled Magnitude Scale.

of consumption of high-fat foods. Of the 40 foods, 29 showed a negative association with fungiform papillae number; these foods formed a statistically reliable group. The number of fungiform papillae ($p < 0.05$) and sex ($p < 0.05$) each contributed to the prediction of fat food intake; BMI did not.

B. Alcohol

Effects of PROP on alcohol consumption were shown by Pelchat and Danowski (74), who reported significantly more nontasters among the offspring of alcoholics than those of nonalcoholics. They suggest that nontasters may not perceive negative sensations from alcohol as a hindrance to overconsumption. The PROP nontasters report the highest beer consumption during the first year of drinking (55) as well as being high consumers (>3.6 L/wk) of beer (75). Despite these findings, there is inconsistent support for PROP and alcoholism associations. In studies identifying PROP tasting by thresholds, Pelchat and Danowski (74) found

a relationship, whereas Kransler and coworkers (76,77) did not. Some of the inconsistency may stem from use of the threshold measure, which, as stated earlier, does not appropriately characterize PROP tasting. In a study with PROP scaling, DiCarlo and Powers (78) found more supertasters among college students who have individual or family problems with alcoholism and depression. However, PROP was rated on a nine-point category scale, which affects the distinction between medium tasters and supertasters (see Chapter 1 in this volume).

Data from the Taste Genetics and Dietary Behavior Study support PROP effects on the reported frequency of alcohol intake (5). Alcohol intake was assessed with the Block Food Frequency Questionnaire as described. Subjects reported their frequency of consuming beer, wine/wine coolers, and liquor/mixed drinks (categories range from "couple of times per day" to "never") and the amount consumed per time. A total annual alcohol intake was calculated from the sum of beer, wine, and liquor consumption. Bitterness of PROP showed a significant negative correlation with total yearly intake of alcoholic beverages. More than half of those who tasted PROP as least bitter reported consuming at least one alcoholic beverage daily. The association between PROP tasting and alcohol intake did not differ in males and females.

C. Salt

Very limited data exist on salt consumption related to PROP status. As part of the Genetic Taste and Dietary Behavior Study, we reported that nontasters were significantly more likely to report "usually" adding salt to food when compared to supertasters (59). The meaning of these adjectives across subjects will differ, making interpretation of these findings difficult. Nonetheless, a subsequent study showed significant associations between NaCl sensation (rated on the gLMS) and sodium intake. In a study of older and young females, greater saltiness and more aversive feelings toward concentrated NaCl in broth associated with lower consumption of sodium assessed by 3 days of food records (68).

VI. GENETIC VARIATION IN TASTE AND SERUM LIPIDS AND BODY COMPOSITION

Fischer and colleagues reported on potential associations between genetic variation in taste and body composition as early as 1966 (79). In the paper

"Gustatory chemoreception in man: Multidisciplinary aspects and perspectives," they state:

> Extremely sensitive tasters of both quinine and 6-*n*-propylthiouracil can be classified as Kretschmerian leptosomes or Sheldonian ectomorphs, whereas the extremely insensitive tasters of both compounds conform to the Kretschmerian pyknic or Sheldonian endomorph type.

Thus, nontasters to quinine and PROP were thought to be of a short, soft, round, and fat body type whereas those with low thresholds to these compounds were thought to have the tall and lean body type. Fischer and coworkers further associated the differences in body type with taste sensitivity through the number of food dislikes.

On the basis of doctoral work, Lucchina (46) described an association between PROP bitterness and body composition as well as serum lipids in a sample of older females at the 1995 AChemS meeting (80). In this study, 60 Caucasian women (mean age, 78 ± 6 years SD, range 65–95 years) who were independent living, reportedly healthy and free of chronic conditions that impose severe dietary restrictions, participated in PROP testing, assessment of body composition, and serum lipid analyses.

The PROP bitterness perception was assessed with magnitude matching (49,57). The subject received verbal test instructions, was questioned to assess comprehension of the procedure, and participated in a practice run using two non-PROP stimuli. Each subject then rated the perceived intensity of randomized auditory (low-frequency, 55–85 dB), orthonasal olfactory (log dilutions of amyl acetate from 0.07%), and PROP solutions (0.0001M–0.0032M). Before tasting the PROP solutions, the women provided magnitude estimates for intensity adjectives (*very weak* to *very strong*). The PROP solutions were presented last to prevent context effects. The PROP ratings were normalized to the geometric mean of each subject's rating of the 85-dB auditory and 0.07% orthonasal stimuli, divided into the arithmetic mean of all geometric means. The normalized 0.0032 M PROP rating was used to compare with body composition and serum lipid data.

Body fat was measured directly by using bioelectrical impedance and indirectly by using BMI calculated from measured height and weight. Waist circumference was measured to provide data on the distribution of body fat. All measurements were obtained in duplicate with the subject wearing very light indoor clothing and no shoes. Fasting blood samples were obtained by a phlebotomist and analyzed for serum total choles-

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terol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, and triglyceride levels (Diagnostic Medical Laboratory, New Haven, CT). Data of women who were prescribed antihyperlipemic medications were excluded from the lipid analyses.

Women who tasted PROP as more bitter had body composition and serum lipids that were more favorable for reduced CVD risk (Table 2). Figure 8 shows that higher PROP tasting correlated significantly with a lower total HDL cholesterol ratio. Cholesterol/HDL ratios above 4.5 suggest an elevated risk of CVD; women who tasted PROP as less than moderately intense were significantly more likely to have a cholesterol/HDL ratio >4.5 (Fig. 8). Total cholesterol did not associate significantly with PROP bitterness. Aged women show elevations in total cholesterol for several years after menopause, which may reflect metabolic changes (81). The relationship between total cholesterol and risk of coronary heart disease in the aged is controversial, unlike the direct relationship between total cholesterol and this risk in younger age groups (82). The HDL cholesterol subfraction and the cholesterol/HDL ratio have strong relationships to the risk of coronary heart disease death in the elderly (83). Elevated triglycerides and lower HDL cholesterol levels can be associated with obesity and with elevated risk of coronary heart disease.

These data support that PROP tasting associated with central adiposity and dyslipidemia, both strong risk factors for CVD. These data

Table 2 Body Composition and Serum Lipid Indices in Aged Females Associated with the Bitterness of 0.0032M 6-*n*-Propylthiouracil[a]

	N	Mean	Desirable range	Standard deviation	Regression coefficient
Body mass index (BMI)	60	28.07	25	4.50	−0.30*
Waist circumference, cm	60	90.32	< 88	11.04	−0.42***
Fat, %	59	34.49		4.77	−0.39***
Total cholesterol, mg/dl	49	231.75	< 200	49.46	0.01
HDL cholesterol, mg/dl	48	49.13	> 45	13.87	0.47***
Total/HDL cholesterol ratio	49	4.99	< 3.5	1.71	−0.37**
LDL cholesterol, mg/dl	48	150.87	< 130	45.03	0.04
Triglycerides, mg/dl	49	158.33	< 150	86.18	−0.46***

[a] HDL, high-density lipoprotein; LDL, low-density lipoprotein; $*p \leq 0.05$; $**p \leq 0.01$; $***p < 0.005$.

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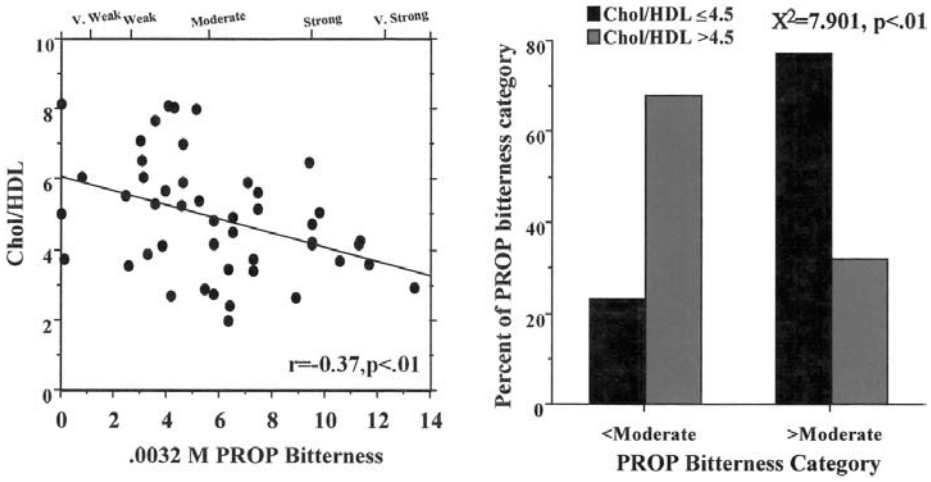

Figure 8 The left panel shows a significant negative relationship between the ratio of total to HDL cholesterol (Chol/HDL) by bitterness of 0.0032M PROP (scaled with magnitude estimate and normalized to a nonoral standard) in aged women. The right panel shows that women who tasted PROP as < "moderate" are statistically more likely to have a ratio of total to HDL cholesterol indicating high CVD risk. HDL, high-density lipoprotein; PROP, 6-*n*-propylthiouracil; CVD, cardiovascular disease.

could not determine whether the PROP effect on CVD was mediated through dietary behavior and thus warranted continued investigation into associations between genetic variation in taste and dietary risk of cardiovascular disease.

The generalizability of the body composition findings of Lucchina and associates (46,80) was tested with a screening for PROP tasting, a PROP impregnated paper, which was originally described by Bartoshuk and associates (9). These data were presented at the 1999 AChemS meeting (44). A convenience sample of lecture participants completed a survey with questions on age, sex, height, weight, and food preferences and rated the perceived bitterness of PROP paper. The seminars, conducted by L. Bartoshuk, took place at institutions of higher learning, industry settings, and social gatherings. The 609 subjects (360 females, 249 males), aged 18 to 92 yrs, were primarily Caucasian and assumed to have a high level of formal education. The gLMS was used for preference and PROP ratings, which were collected before each lecture. With these data, we examined the

association between PROP bitterness and the degree of liking/disliking of nine high-fat foods as well as BMI. These high-fat foods (cheddar cheese, whipped cream, whole milk, buttered popcorn, sausage, butter, mayonnaise, sour cream, and pecan pie) formed a statistically reliable group (Cronbach's alpha = 0.73).

These data showed both sex and age influences on PROP tasting (44). A taster classification defined 122 nontasters, 318 medium tasters, and 169 supertasters on the basis of the criteria that nontasters taste concentrated PROP as less than "moderate" and supertasters taste it as more than "very strong." Across the entire sample, females were significantly more likely to be supertasters and males more likely to be nontasters ($\chi^2 = 20.278$, $p < 0.0001$). This sex difference did not hold true in those above the age of 50 years. Within the female group, women older than the age 50 years were significantly more likely to be nontasters ($\chi^2 = 11.561$, $p < 0.01$). Age effects on PROP tasting have also been reported by Lucchina (46).

6-*n*-Propylthiouracil bitterness showed a significant negative association with BMI, but not in those subjects who were obese (BMI > 30). Tepper and Ullrich (84) suggest that dietary restraint and disinhibition may influence the relationship between PROP and BMI in the obese. The influence of age, sex, and PROP on those subjects who had a BMI that was "normal" (17 to 25) or "overweight" (25 to 30) was examined. Subjects older than age 50 were excluded from the analyses because of age effects on PROP bitterness. Standard multiple regression analysis was performed, identifying univariate and multivariate outliers (85). The multiple *r* was 0.49 (adjusted $R^2 = 0.24$, $p < 0.0000001$) with PROP bitterness, age, and sex as significant predictors (Fig. 9). The PROP bitterness also showed a significant negative association with degree of liking/disliking of high-fat foods but only in females. In females, PROP, age, and BMI each contributed significantly to prediction of liking of high-fat foods.

The Taste Genetics and Dietary Behavior Study allowed a preliminary examination of the hypothesis that nontasters showed a greater risk of CVD than did supertasters (86) and that the risk was, in part, expressed through diet. Risk of CVD was defined in this study by dietary behavior toward high-fat foods as well as serum lipids. In order to maximize the sensory differences, we took the strategy of defining the extremes of variation in taste genetics with both PROP bitterness and density of fungiform papillae.

The PROP tasting was defined with the PROP ratio (23) using PROP and NaCl intensity scaled with the gLMS. This classification appropriately ranks taster status from lowest to highest, as supported by Bartoshuk and

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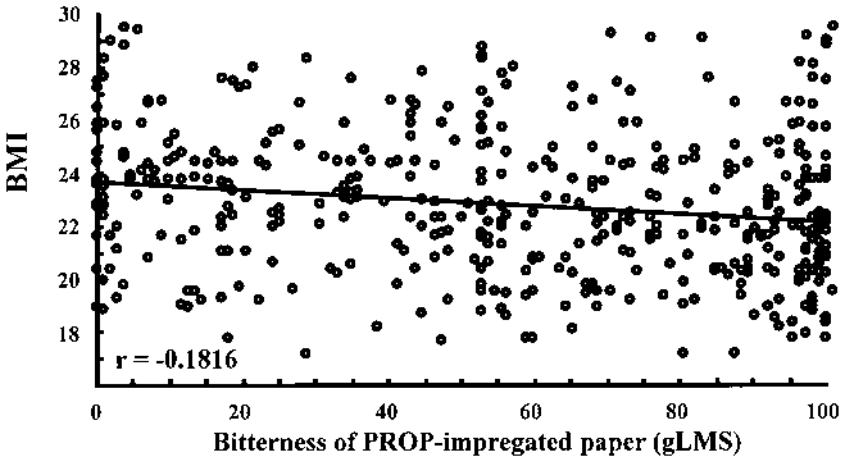

Variable	Partial Correlation	t(437)	p-level
SEX (1=F;2=M)	0.377	8.67	0.0000000
AGE	0.298	7.01	0.0000000
PROP Bitterness	-0.091	-2.06	0.040

Figure 9 The association between body mass index (BMI) and the bitterness of PROP-impregnated paper (rated on the gLMS) in adults aged 18 to 50 who are normal and overweight according to the BMI ($17 < \text{BMI} > 30$). The table shows the partial contributions of sex, age, and PROP bitterness to prediction of BMI. PROP, 6-*n*-propylthiouracil; gLMS, general Labeled Magnitude Scale.

associates (see Chapter 1 in this volume). The PROP ratio is the bitterness of PROP (*P*) standardized to the saltiness of sodium chloride (N):

$$[(0.001P/0.32\text{N}) + (0.0032\text{P}/1\text{N})]/2$$

Nontasters had a ratio <0.4 and supertasters ≤ 1.2 (23). High number of papillae was defined as >25 papilla per 6-mm area, low as ≤ 25 papillae. Figure 10 shows the groups of 16 nontasters and 17 supertasters defined by PROP ratio and fungiform papillae number. The females were more likely than the males to be supertasters ($p < 0.05$). The nontasters and supertasters did not differ in measures of absolute (BMI) or relative (waist/hip circumference) obesity (Table 3).

Dietary fat intake was assessed by how frequently subjects reported consuming 40 high-fat foods (as reported previously) as well as five daily

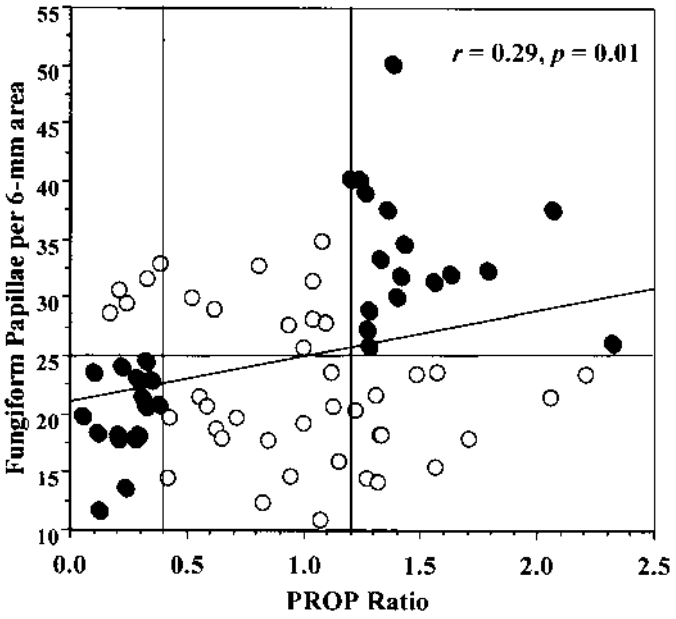

Figure 10 PROP bitterness (ratio of PROP bitterness over NaCl saltiness) by number of fungiform papillae (FP) to show two discrete groups. Nontasters (n = 16) have low PROP ratios and low FP number; supertasters (n = 17) have high PROP ratios and high FP number. There were significantly more females in the supertaster (12 females, 5 males) than in the nontaster (5 females, 11 males) group (Fisher's exact, $p < 0.05$). PROP, 6-*n*-propylthiouracil.

Table 3 Age, Absolute (BMI), and Relative (waist/hip ratio) Obesity in Nontaster and Supertaster Groups[a]

	Nontasters (n = 16)		Supertasters (n = 17)		All (n = 33)	
	Mean	SEM	Mean	SEM	Mean	SEM
Age	26.0	0.7	27.7	1.2	26.9	0.8
BMI	23.4	0.7	23.0	0.7	23.2	0.5
Waist/hip ratio	0.79	0.02	0.8	0.02	0.8	0.01

[a] Measured in 33 young adults and those separated into NT and ST groups by the bitterness of 0.0032 M PROP and the density of fungiform papillae. SEM, standard error of the mean; BMI, body mass index.

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food records (collected on nonconsecutive days). A registered dietitian trained the subjects to keep food records and reviewed the records to clarify portion sizes and specific foods consumed. The dietitian also completed the dietary analysis with the Food Processor Program, Vers. 7.5, ESHA Research, Salem, Oregon. A one-tailed *t*-test and the chi square statistic were used to examine mean and/or distribution differences in fat variables between nontasters and supertasters.

The individuals classified as nontasters had significantly higher average total cholesterol, LDL cholesterol, and fat intake than those classified as supertasters (Table 4). The distribution of TC/HDL ratio was significantly different in the two groups. Individuals who were high on both genetic taste measures were more likely to have a TC/HDL ratio below 3.35 than were those who were low on both measures ($\chi^2 = 4.04$, $p < 0.05$). The lack of statistical power due to small sample size does not allow for the control of both genetic taste and sex effects. Nonetheless, these data support the findings of Lucchina and associates (46,80) in that individuals who taste PROP as least bitter have serum lipid levels that increase the risk of CVD. The pattern of association between PROP and the lipids differed in the two groups. In aged women, there are complex interactions between aging and lipid metabolism that challenge the interpretation of taste genetic influences on serum lipids. Data from younger subjects provide preliminary support for the hypothesis that taste genetic

Table 4 Fat Intake and Serum Lipid Levels in Young Adults from the Taste Genetic and Dietary Behavior Study[a]

	Low PROP, low FP ($n = 16$)	High PROP, high FP ($n = 17$)
Yearly intake of 40 high-fat foods*	2232.25 ± 319.30	1609.18 ± 176.49
Percentage fat calories*	30.96 ± 1.04	27.32 ± 1.70
TOT. CHOL (TC)*	181.65 ± 7.21	161.07 ± 6.21
TC/HDL†	4.03 ± 0.31	3.39 ± 0.20
HDL	47.82 ± 2.84	48.73 ± 2.22
LDL*	106.94 ± 4.82	89.27 ± 6.77
TG	124.41 ± 22.03	115.67 ± 18.39

[a] PROP 6-*n*-propylthiouracil; TOT. CHOL, total cholesterol; TC, total cholesterol; HDL, high-density lipoprotein; LDL, low-density lipoprotein; FP, *$p < 0.05$; †$p < 0.1$.
Source: Ref. 86.

influences on serum lipids work through dietary behavior toward high-fat foods.

VII. SUMMARY

Cardiovascular disease is a significant public health problem. Diet plays a role in preventing CVD through modifying the quantity and quality of fat consumed and avoiding alcohol and salt overconsumption. Despite public health efforts in developed countries such as the United States, individuals are not adhering to diets that minimize CVD risk, perhaps because of ready access to an array of good-tasting high-fat sweet and salty foods. Genetic susceptibility can explain a sizable portion of the variance in palatability and may influence risk of overconsumption, especially in an environment of readily available palatable and high-fat foods (87).

This chapter presents data to support genetic influences on CVD risk that are expressed through dietary behaviors. Consumers report that the taste of foods and beverages is a primary determinant of what they eat. The term *taste* refers in this context to true taste, as well as retronasal olfactory and oral somatosensations. Oral sensations from foods and beverages vary with two markers of genetic variation in taste, the bitterness of PROP and the density of fungiform papillae on the anterior tongue. Those who taste minimal bitterness from PROP and/or have the lowest number of fungiform papillae report less intensity from tastants, less tactile sensation from fat, like high-fat foods and beverages more, and consume high-fat foods more frequently. In the 1960s, Fischer and colleagues proposed the idea that these "nontasters" would have a heavier or stockier build because of their dietary behavior. This concept is supported by data in this chapter and that of Tepper and colleagues. The nontasters, defined by PROP bitterness or by PROP bitterness and fungiform papillae, also have body composition and serum lipid profiles that increase the risk of CVD, as shown in samples of older women and young adults.

There appear to be genetic influences on alcohol, and possibly salt, behavior. Consumption of alcoholic beverages can enhance dining experiences and actually lower CVD risk in amounts recommended by public health guidelines such as the Dietary Guidelines for Americans. However, excessive consumption of alcohol increases risk of high blood pressure and thus CVD risk. Alcohol can present unpleasant sensations of bitterness and burn; individuals who taste PROP as more bitter report these unpleasant sensations as more intense than those who taste PROP as less bitter.

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There are some data to support that for the PROP supertaster, alcohol may present enough of an unpleasant oral sensation to act as a sensory hindrance to overconsumption. Salt is a condiment that may mask bitterness of foods. Excessive intake of salt or sodium can increase the risk of high blood pressure, especially in those who are sodium-sensitive. Concentrated salt can present unpleasant sensations of irritation in addition to salty taste. Those who taste PROP as more bitter report greater intensity from concentrated salt in solution as well as broth. It is plausible that the PROP supertaster may be more equipped to perceive the negative oral sensations from concentrated salt in food or beverage systems as a way to prevent overconsumption of sodium. However, many processed foods and beverages contain sodium that is present without an apparent salty taste.

The opportunity exists to continue exploring associations between genetic variation in taste and risks of chronic diseases such as CVD. The findings presented here are preliminary and warrant further investigation. Continued investigation is needed to show that taste genetics associate with CVD risk and that the risk is expressed through dietary behaviors. This research would require increased numbers of subjects to test hypothesized relationships with causal models such as path analysis (88). Other research would test the generalizability of the findings in larger samples and examine additional markers of CVD risk. The eventual aim of this research is to increase our ability to impact the quality of an individual's diet to reduce chronic conditions while maintaining the enjoyment of eating.

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11

6-*n*-Propylthiouracil Taster Status
Dietary Modifier, Marker, or Misleader?

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I. INTRODUCTION

The study of taste responsiveness to 6-*n*-propylthiouracil (PROP), phenylthiocarbamide (PTC), and other thioamide-containing compounds has yielded an array of proven and promising insights. The strong genetic basis for sensitivity to these compounds has provided a tool to anthropologists for tracing family lineages and population migration patterns. There are well over 400 reports in the anthropology literature using this tool (1). Taste responses to PROP/PTC have also been linked to various health disorders. There are instances in which a causal association has been proposed [e.g., goiter (2), alcoholism (3, 4), selected cancers (5)]. More commonly, bitter sensitivity has been regarded as a marker of risk (e.g., schizophrenia, depression, vascular headache, duodenal ulcer, glaucoma, tuberculosis, leprosy, Down syndrome (6) or progression [e.g., diabetes (7), hypothyroidism (8)] of selected health disorders or of sensitivity to therapeutic agents (9). Although confirming data are lacking in each of these examples, the use of taste as an index of disease risk or marker of disease progression or remission holds promise. Associations between taste responses to PROP/PTC and various personal characteristics [e.g., selected subscales of the Wechsler Adult Intelligence Scale (10)], visual motor

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function (2), and body habitus (9) have been documented as well. If verified, this may provide perspectives on individual behavior and performance. More recently, interest in individual differences in sensitivity to PROP has prompted research that has resulted in improved understanding of the multiple transduction mechanisms for bitterness (e.g., 11,12). This emerging knowledge holds implications for understanding of basic biological processes as well as product development by the food and pharmaceutical industries.

An additional area of study, and the focus of this chapter, concerns the role of PROP/PTC taste sensitivity/responsiveness as a determinant of food choice and energy balance. Interest in this topic has largely stemmed from hypotheses regarding the ecological significance of bitter taste. Most commonly, it is argued that bitter sensitivity serves as a mechanism for detecting and rejecting toxins. Thus, individuals sensitive to the bitter notes in foods should be more likely to avoid them. Early work examined this notion by classifying individuals as PROP/PTC nontasters or tasters and contrasting the number of foods they disliked. This classification was followed by hypotheses linking taste, food choice, and disease risk. Initially, it was assumed that insensitivity to PROP/PTC was indicative of insensitivity to unhealthful bitter substances in foods, and this insensitivity played a permissive role in their consumption. One example is the hypothesis that the ingestion of bitter goitrogens would be higher among PROP/PTC nontasters, resulting in a higher incidence of goiter (2). Another example is the purported increased risk of alcoholism among nontasters due to a higher acceptance of the bitterness of alcohol (3). Alternatively, it has been posited that sensitivity to healthful bitter compounds in foods may predispose individuals to health disorders. A current hypothesis holds that consumption of cruciferous vegetables containing various bitter phytochemicals reported to reduce the risk of certain cancers will be lower in PROP tasters (5). Each of these scenarios is reasoned, plausible, and, most importantly, testable.

The data pertaining to such hypotheses are critically reviewed in this chapter. There are numerous abstracts of work in this area, but only published, peer-reviewed papers are included. An objective assessment is required to ensure that appropriate dietary guidelines are developed. Modification of customary dietary practices can have unintended adverse nutritional and behavioral consequences and would be ill advised if based on fallacious associations. At the same time, failure to recognize a meaningful association could mean the loss of an opportunity to optimize dietary practices.

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II. GENERAL CONCERNS

Despite the intuitively appealing arguments supporting a regulatory role for bitter taste in human feeding, as reflected by sensitivity or responsiveness to PROP, there are a number of conceptual and practical issues that challenge or might mitigate this function. Thus, identification of an influence may be problematic. First, it has been proposed that the inherent low palatability and rejection of foods with bitter notes stem from selective evolutionary pressures (13). Because many toxins are bitter, those who were more sensitive to bitterness and inclined to avoid bitter substances were more likely to contribute to the gene pool. If true, the present-day high proportion of nontasters is problematic. In some populations, nontasters constitute the majority [e.g., Southern Indians (14)] and in others, the distributions of nontasters and tasters are similar [e.g., Northern Aborigines (15)]. One explanation for the existence of nontasters may be that insensitivity also holds advantages. The willingness to ingest items with bitter notes would expand the diversity of acceptable foods (16). It is a long-held dietary tenet that variety promotes consumption of more nutritionally balanced diets (17,18). Further, accumulating evidence suggests that many foods with bitter notes contain health-promoting substances (5). Thus, arguments can be made that sensitivity and insensitivity to bitterness are beneficial. As a consequence, the predictive value of bitter taste for food choice would be compromised.

Second, the apparent innate dislike for bitterness (19,20) can be modified through dietary experience. Bitter foods may be more resistant to a hedonic shift promoted by repeated exposure than novel sweet or salty items (21), but preferences can develop. A preference for sourness and bitterness has been documented among Indian laborers accustomed to eating foods with these qualities relative to members of the same population adhering to more Western diets (22). Indeed, many foods with prominent bitter notes, such as coffee, tea, chocolate, alcohol, various leafy greens, as well as certain cruciferous vegetables and fruits, are highly preferred. The reasons for the high acceptability of these foods are multiple, ranging from health beliefs and psychoactive effects to their sensory properties. Bitterness may have limited appeal in model solutions, but it is an important component of a food's flavor and, as a consequence, enhances rather than detracts from the appeal of many foods. The acquisition of a preference for overtly bitter foods and appreciation of their complex mix of flavor components, such as occur with wines, would

further confound attempts to identify associations between bitter perception and food choice or nutritional indices.

Third, the sensory properties of foods are frequently modified during preparation according to one's cultural practices. In the United States, it is common to add sugar and/or milk to coffee and tea; salt and/or butter to vegetables; sweet, salty, or sour mixers to alcohol, and salad greens are mixed with or covered by ingredients of various flavors. Thus, an item's inherent bitter property may be masked through customary food preparation practices. Such practices would likely obscure the influence of individual differences in bitter sensitivity on food choice.

Fourth, there is evidence that PROP sensitivity is stable throughout aging (23). Other data suggest that sensitivity declines after age 20 (24), but this shift may be due to factors associated with aging such as cumulative smoking exposure (25,26). In contrast, shifts of food preference, choice, and nutrient intake over the life cycle are widely recognized (27–29). As a result, any relationship between PROP taster status and food preferences or diet will be in flux and difficult to quantify.

Fifth, flavor is only one of a multitude of factors guiding food choice (30). Taste is only a small contributor to flavor, and sensitivity to PROP and related compounds is only one facet of taste. Thus, attempting to quantify a contribution of PROP taster status to ingestive behavior would be analogous to looking for a needle in a hay stack. Of course, if one steps on the needle in the course of exploration, it becomes highly salient. Thus an influence of bitterness, as indexed by PROP taster status, cannot be dismissed.

Although these general observations argue against a meaningful association between bitter taste and food choice, ultimately data from controlled studies will be most telling. For PROP sensitivity to be a useful predictor of food choice and nutritional status, several lines of evidence must be established. These include documentation that sensitivity to PROP is associated with (a) sensitivity or responsiveness to bitter and/or other compounds in food, (b) hedonic responses to foods, (c) food intake and (d) body weight or composition.

III. 6-*n*-PROPYLTHIOURACIL TASTER STATUS AND SENSITIVITY/RESPONSIVENESS TO VARIOUS FLAVOR COMPOUNDS

The importance of establishing an association between PROP taster status and sensitivity or responsiveness to other sensory stimuli in foods is fun-

damental to the view that taster status is linked in some causal way to food choice. If taster groups do not perceive flavor compounds differently, there would be little rationale for sensory-based differential ingestive responses. The most direct association would be through bitter compounds. There is a family of 40–80 likely bitter receptors (31–33). Further, taste receptor cells may express multiple receptor types, and single receptors may respond to more than one bitter compound (e.g., PROP and denatonium benzoate). These findings are a double-edged sword for the hypothesized link between PROP sensitivity and diet. On one hand, they provide a basis for independent responsiveness to the vast array of bitter compounds in foods. Thus, it cannot be assumed that bitter sensitivity is a generalized characteristic of an individual. Alternatively, they support the possibility that structurally similar compounds elicit comparable bitter responses (12). This is a critical point given that PROP is not a food constituent. Indeed, because there could be no selective pressure for preserving sensitivity to PROP, its association with the bitterness of food-borne compounds can only be fortuitous (34). A large number of studies have compared taste responses to PROP with ratings for other bitter compounds in model systems, foods with clear bitter notes or model solutions or foods with other taste qualities.

Most commonly, studies of isolated bitter compounds have contrasted responses of PROP taster subgroups for quinine, caffeine, or urea. They have yielded mixed results (see 11). A 2001 trial (11) expanded this search by obtaining bitterness intensity ratings for 10 compounds, many of which are present in foods, as well as PROP on a labeled magnitude scale. Application of cluster analysis to intensity-normalized ratings revealed four clusters, one containing urea, phenylalanine, tryptophan, and epicatechin; a second composed of quinine, caffeine, sucrose octaacetate, denatonium benzoate, and tetralone; and two more including only magnesium sulfate or only PROP. Analyses based on PROP nontasters and supertasters revealed differences in absolute bitterness ratings, but not with respect to their relative sensitivities to the test compounds. These findings are in general agreement with earlier work (35–37), particularly in regard to the independence of PROP sensitivity. Others have begun to explore the association between responses to PROP and various phytochemicals. The PROP taster subgroups do not rate the bitterness of naringin solutions differently (38). Thus, the literature offers only limited support for a reliable association between bitterness ratings for PROP and those for other bitter substances in model systems.

More ecological studies have explored the association between PROP taster status and perceived bitterness of foods generally regarded

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as having prominent bitter notes. Most work has not revealed differences. Niewind and coworkers (39) observed no differences between PTC tasters and nontasters for the bitterness of cabbage, but tasters did rate the overall flavor differently. Similar bitterness ratings based on questionnaire responses were reported by Mattes and Labov (40) for 31 foods with and without goitrogens; by Jerza-Latta and coworkers (41) for 11 sampled cruciferous and two noncruciferous vegetables; by Akella and colleagues (42) for samples of plain soy milk, vanilla-flavored soy milk, miso, or plain tofu; and by Ly and Drewnowski (43) for tasted milk chocolate. In contrast, Akella and colleagues (42) reported supertasters rated the bitterness of green tea higher than tasters or nontasters, and Intranuovo and Powers (4) found supertasters rated the bitterness of one of two types of beer as stronger than tasters and nontasters.

In 2002, we asked 317 individuals to taste samples of fresh grapefruit, raw cabbage, brewed green tea, and chocolate (Hershey's semisweet milk chocolate, Hershey Food Corp, Hershey, PA). They also smelled samples of fresh grapefruit, boiled cabbage, brewed green tea, chocolate, baby powder, and tobacco. Participants were classified as nontasters, tasters, or supertasters if they rated the taste of a solution of 0.32mM PROP as $<$15.5 mm, between 15.5 and 51 mm, or $\geq$51 mm, respectively, on a 100-mm labeled magnitude scale (44). The upper label of the scale was "strongest imaginable" taste or oral stimulus ever experienced. Because of concern about the ability of children to use the response scale, all analyses were conducted on the full sample as well as subsets composed of individuals older than 18 or 21 years of age. Results did not differ. Participant characteristics are listed in Table 1. Rated bitterness for the PROP solution was significantly positively correlated with rated

Table 1 Sex, Age, and Body Mass Index Characteristics of Participants Classified as Nontasters, Tasters, or Supertasters[a]

	Nontaster	Taster	Supertaster
Sex (M/F)	35 / 62	51 / 90 (1 N/A)	24 / 54
Age, years	25.8 ± 1.6	27.4 ± 1.4	32.7 ± 2.2
[range]	[10–76]	[10–77]	[10–79]
BMI, kg/m^2	24.0 ± 0.6	24.6 ± 0.5	25.6 ± 0.7

[a] Classifications are based on ratings of 0.32mM PROP as $<$15.5 mm, between 15.5 and 51 mm or $\geq$51 mm on a 100-mm labeled magnitude scale, respectively. BMI, body mass index; PROP, 6-*n*-propylthiouracil; N/A, not available.

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bitterness of grapefruit ($r = 0.33$, $p < 0.001$), cabbage ($r = 0.16$, $p < 0.01$), tea ($r = 0.24$, $p < 0.001$), and chocolate ($r = 0.89$, $p < 0.001$). Analysis of variance (ANOVA) revealed significant taster group differences wherein the three groups differed for grapefruit and chocolate and the supertasters rated the bitterness of tea stronger than did nontasters and tasters (Fig. 1). There was no group difference for ratings of cabbage. Consistent correlations were also observed between rated taste intensity of PROP and odor intensity of the samples. The values were as follows: grapefruit ($r = 0.28$, $p < 0.001$), cabbage ($r = 0.16$, $p < 0.05$), tea ($r = 0.28$, $p < 0.001$), chocolate ($r = 0.34$, $p < 0.001$), tobacco ($r = 0.15$, $p < 0.05$), and powder ($r = 0.30$, $p < 0.001$). Significant taster group differences were observed for all samples except the cabbage (Fig. 1). Supertasters rated the odor stronger than did nontasters for the grapefruit, tea, and tobacco. All three groups differed in ratings for the chocolate, and the supertasters rated the odor of the baby powder as stronger than either nontasters or tasters did. Intensity ratings for bitter taste were significantly correlated with odor intensity ratings for each food stimulus (grapefruit, $r = 0.30$, $p < 0.001$; cabbage, $r = 0.175$, $p < 0.005$; green tea, $r = 0.40$, $p < 0.001$; chocolate, $r = 0.34$, $p < 0.001$). These data demonstrate that taster status is associated with reported bitterness in selected foods (no difference was noted with cabbage) but raise a question about the nature and specificity of the stimulus being evaluated. As in nearly all published work, taste ratings were not obtained with the nares closed. Given that the taste and odor ratings were significantly correlated, it is possible that the bitterness ratings reflected differences in odor perception. Similarly to our findings, Niewind and colleagues (39) noted that taster and nontaster groups did not differ in bitterness ratings for cabbage but did differ in overall flavor intensity. Yackinous and Guinard (45) report greater sensitivity to a pure odor (diacetyl) by tasters and supertasters when compared to nontasters. The potential for other sensory attributes to contribute to reported taste responses to foods should be better controlled in future work. Taken together, the data presently do not clearly support PROP taster differences in bitter taste ratings of foods with bitter notes.

The association between PROP status and perceived intensity of other taste qualities in model solutions has yielded mixed results. Saltiness was regarded as independent of PROP sensitivity and has been used extensively as a control stimulus for taster classification (44). However, there are data indicating that the taste of NaCl is more intense to supertasters (46).

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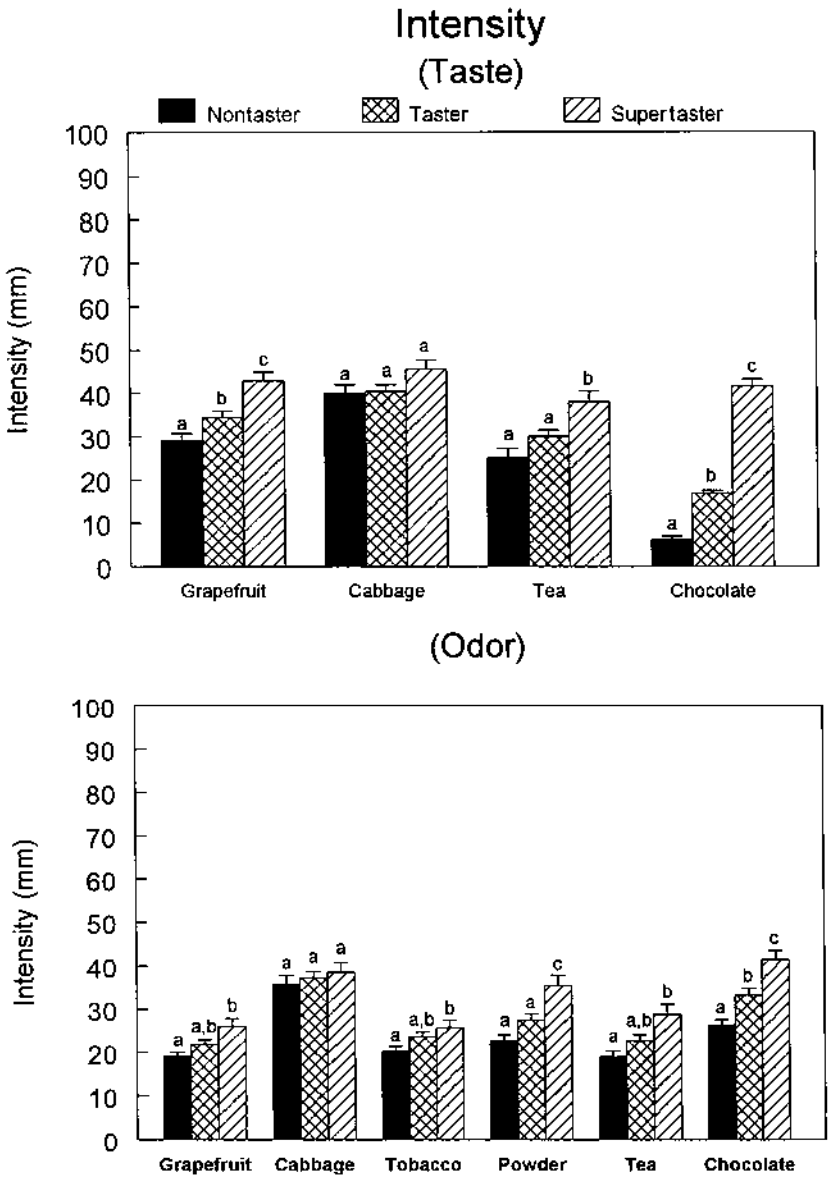

Figure 1 Taste and odor intensity ratings of nontasters, tasters, and supertasters for fresh grapefruit, raw cabbage (taste), boiled cabbage (odor), brewed tea, semisweet chocolate; tobacco (odor only), and baby powder (odor only). Ratings for each food with different superscripts are significantly different. Ratings were made on a general labeled magnitude scale.

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Sweetness has been assessed extensively. In a review of 16 studies (47), 11 observed an association with PROP classification and five did not. The variability was attributed to methodological differences. It was noted that among the early studies, in which PROP classification was based only on divisions of nontasters and tasters, five observed higher ratings by tasters and two reported no differences. Eight studies used a three-PROP taster group classification but may have been hampered by context and ceiling effects. Only three of these studies were peer-reviewed reports. Among these, one found a positive association, and two did not. Unfortunately, not one of the four trials that used classification methods that reportedly control response bias has appeared in a peer-reviewed publication. Work that was not included in the review (48) or that was published after the release of the review (43,45) has challenged the view that sweetness is differentially perceived by individuals across PROP taster groups. In sum, there is suggestive evidence of group differences in sweet perception, but inadequate data on which to draw a definitive conclusion.

Considerably less work has addressed the question of whether PROP taster status is linked to perception of selected stimuli in food systems. One line of research has focused on dietary fat. The rationale has been that fat is primarily detected on the basis of its textural properties and there may be a direct association between PROP taste sensitivity and trigeminal innervation of fungiform papillae (47). However, there also is accumulating evidence for a taste component to dietary fat in humans (49,50). The first published data on this issue revealed that PROP tasters and supertasters were able to distinguish between salad dressings containing 10% and 40% fat whereas nontasters could not (51). In 2001, Nasser and coworkers (52) noted that 8/10 PROP tasters but only 1/6 nontasters could identify a sample of ice cream with added conjugated linoleic acid relative to control ice cream in a one-trial test. In contrast, Kamphuis and colleagues (53) detected no differences in ability to discriminate between oils relatively high in linoleic acid, gamma-linolenic acid, or oleic acid among participants classified by taster status. Drewnowski and coworkers (54) observed no intensity response differences to a matrix of 15 sugar–fat mixtures among females classified as nontasters, tasters, or supertasters. Most recently, Yackinous and Guinard (45) noted no PROP taster differences in fat judgments for potato chips, chocolate drink, mashed potatoes, and vanilla pudding. Findings from these latter two studies do not necessarily conflict with those of the former two since they were based on intensity ratings instead of discrimination responses. Whether there is a difference in fat perception among individuals classified by PROP taster status and on

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what basis (i.e., taste, odor, texture) any distinction may be made, remains to be resolved.

The less than compelling body of evidence supporting differential sensitivity or responsiveness to bitterness or other qualities in model systems or foods among PROP taster groups poses a problem for the view that this classification reflects true sensory differences among individuals that influence food choice. Following the hypothesis further requires acceptance that sensorily based hedonic judgments may occur independently of stimulus detection or rated intensity or that the literature reviewed previously is largely flawed methodologically. There are several cases of the former situation (38,51,55), and the latter view has been proposed (47,56,57).

IV. 6-*n*-PROPYLTHIOURACIL TASTER STATUS AND HEDONICS

Because model systems have limited dietary relevance, only studies exploring the hedonic responses of PROP taster groups to foods are assessed here. It is unlikely that this restriction will distort an interpretation of current knowledge since findings from model systems such as sweet solutions (e.g., 58,59) are conflicting. Early studies were based only on a nontaster–taster classification and responses to questionnaires requesting information about food likes and dislikes. Arbitrarily defining 48 students as having a low or high level of food dislikes on the basis of whether they disliked 0% to 10% or 10% to 55% of items on a list of 118 foods, Fisher and colleagues (60) noted an inverse relationship with PROP threshold. Glanville and Kaplan (61) used a questionnaire eliciting information on preparation or variety preferences of coffee, cheese, and salad dressing (generally bland to strong flavored) of 187 adults and noted an indirect relationship with PROP threshold. Later studies using food lists were less successful in identifying an association with PROP taster status. Jefferson and Erdman (62) observed no relationship between PROP threshold and hedonic ratings for 54 foods commonly consumed in the test area by 45 13- to 14-year-olds. Drewnowski and coworkers (55) reported significant inverse associations between PROP thresholds and hedonic ratings for three of six vegetables, zero of seven sweets and desserts, and two of three beverages (both coffee) among 150 women using a 171-item food list. On the basis of intensity ratings for PROP, associa-

tions were observed for two of six vegetables, one of seven sweets, and two of three beverages (both coffee). Only three of the significant associations based on threshold sensitivity also held when intensity judgments were the basis of PROP characterization and all correlations were ≤ 0.27. In a subsequent study, the same food list was used to obtain ratings from women who were healthy or diagnosed with breast cancer (63). Higher acceptance of cruciferous vegetables, green vegetables, and raw vegetables, but not of fruits was reported by supertasters as compared to nontasters. However, the correlations ranged from 0.11 to 0.19, so taster status accounted for less than 4% of the variance in hedonic ratings. Duffy and Bartoshuk (56) asked 24 women and 22 men to rate 83 foods for acceptance and observed an inverse association with sweets ($r = -0.3$), but no significant correlation with fruits, natural sweets, low-calorie sweets, an average of sweet items, two groups of high-fat items, cheese, an average of high-fat foods, vegetables, cruciferous vegetables, bitter beverages, or an average of bitter items. Significant associations were observed for selected items in the sweet and fat categories in separate analyses of males and females, but no associations with bitter items were identified in either sex.

For a variety of reasons, food lists yield only qualitative information on food preferences. First, lists preclude the ability to test foods as they would actually be prepared and consumed by individuals. So, ratings are based on personal history, which varies across study participants. Second, there is no control over whether the foods are familiar to each study participant or whether a chosen list captures his or her general hedonic orientation. Third, lists do not control context effects such as the timing and circumstances of consumption. Unfortunately, there have been no attempts to test the reliability or validity of the responses obtained to date. Participant sampling of foods under controlled conditions helps to standardize the task.

Table 2 summarizes the published data on the association between PROP taster status and hedonic responses to sampled foods. The preponderance of findings from these studies do not support a significant association across a range of items. Where positive associations are noted, their interpretation is uncertain. In the trial by Anliker and collegues (64), a significant relationship was observed for only two of eight foods on one of three hedonic tests, and the results were in opposite directions for these two items. Cheese was favored and milk was less preferred by nontasters. Akella and colleagues (42) report a significant association between PROP taster status and ratings for two of four soy

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Table 2 Summary of Published, Peer-Reviewed Data on the Hedonic Ratings of Sampled Foods by Individuals Classified Variously by Different Researchers as Nontasters, Tasters, or Supertasters[a]

Author, Yr (Ref)	PROP classification	Subjects	Index	Findings PROP Taster Groups[a] (NT = nontaster; T = taster, ST = supertaster)
Niewind et al., 1988 (39)	PTC Threshold Staircase method	32 ♀ 55–70 yr	15 cm Line scale	NS
Anliker et al., 1991 (64)	PROP threshold PROP/NaCl ratio Adapted 5-pt category scale	34 5–7yr	Rank order 5-pt category scale 60 item questionnaire	NT favor cheese—rank data T favor milk—rank Data Category scale ratings—NS Fd. pref questionnaire—NS
Drewnowski et al., 1997 (38)	PROP threshold PROP/NaCl ratio 9-pt category scale	123 ♀ 20–60 yr	9-pt category scale	Naringin in $H_2O \pm$ sucrose ST > pooled NT + T Grapefruit juice NT > ST Grapefruit juice—NS Lemon—NS Orange—NS Orange juice—NS Apple—NS
Akella et al., 1997 (42)	PROP threshold PROP/NaCl ratio 9-pt category scale	53 ♀ 20–45 yr	9-pt category scale	Tofu—NT > ST Sweet vanilla soy milk—ST > NT Plain soy milk—NS Miso—NS Green tea—NT < T, ST
Intranuovo and Powers, 1998 (4)	PROP paper labeled magnitude scale	100 21–49 yr	9-pt category scale	Beer—NS (♂ ST< T, NT only if dark beer sampled after lighter beer)
Drewnowski et al., 1998 (54)	PROP threshold PROP/NaCl ratio 9-pt category scale	118 ♀ 20–40 yr	9-pt category scale	Sugar–fat mixtures—NS
Tepper and Nurse, 1998 (65)	PROP/NaCl ratio 15-cm line scale	75 18–51 yr	9-pt category scale	40% Fat dressing—NT > T, ST
Ly and Drewnowski, 2001 (43)	PROP paper PROP solutions 9-pt category scale	54 ♀ 18–30 yr	9-pt category scale	Three types of chocolate—NS Coffee—NS
Keller et al., 2002 (66)	1 PROP solution Y or N response	67 4–5 yr	5-pt facial scale	Raw broccoli—NT > T Cooked broccoli—NS Orange juice—NS Orange/grapefruit juice—NS Semisweet chocolate—NS Milk chocolate—NS Whole milk—NT ♀ > T ♀ Fat-free milk—NS American cheese—NT > T American cheese—sharp—NS Beef hot dogs—NS Turkey hot dogs—NS

[a] NS, no significant differences between PROP taster groups; PROP, 6-*n*-propylthiouracil; PTC, phenylthiocarbamide; Fd. pref.

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products, and again the ratings are in opposite directions for the two items. Nontasters rated sweetened vanilla soy milk lower, but tofu higher than supertasters. Drewnowski and colleagues (38) observed an association between PROP taste sensitivity and ratings for only one of six fruit and fruit juice samples. Tepper and Nurse (65) acknowledge the quandary posed by their data, which indicate that nontasters prefer salad dressing that is 40% fat but are unable to discriminate between this sample and a version containing only 10% fat. Thus, the basis of this hedonic rating is uncertain. Duffy and Bartoshuk (56) found a significant effect only for sweets and not eight other food categories including those for which other researchers noted effects [e.g., fruit (38), cheese (64), fat (65)]. The association between taster status and ratings of beer revealed no differences except that male supertasters rated a darker beer as less pleasant after they had previously sampled a lighter beer (4). Finally, Keller and colleagues (66) reported a higher liking of raw broccoli and American cheese from an array of 12 foods by 3- to 4-year-old nontasters as compared to tasters, but with correction for multiple testing, these were not significant. Thus, their data again conflict with those of several earlier reports. In addition, the collective data based on sampled foods are not consistent with reports of significant associations based on surveys using food lists. Whereas those surveys noting significant effects suggested reduced acceptability of bitter beverages, cruciferous vegetables, and cheese to PROP-sensitive individuals, this finding was not confirmed when participants actually sampled the items.

Despite differences in intensity judgments by PROP taste groups, hedonic ratings from our 2002 trial (described previously) also reveal no group differences (Fig. 2). Ratings were similar for the pleasantness of the taste for fresh grapefruit, raw cabbage, brewed tea, and semisweet chocolate as well as for the odor of these items, tobacco, and baby powder. Interactions among food pleasantness ratings, PROP taster status, and sex, age, or body mass index (BMI) were all nonsignificant. It may be argued that hedonic ratings in a laboratory setting also are imperfect since they are obtained in "nonnormal" environments and for only a small array of items that may not be presented in customary ways. The addition of seasonings and condiments can reduce or eliminate differences in hedonic judgments for unadulterated foods by PROP tasters and nontasters (43). The optimal method for assessing food preferences has yet to be identified. Concerns have been raised about PROP taster classification approaches; however, methodologies for evaluating flavor preferences are equally problematic. Hedonics is a multidimensional attribute. Information ob-

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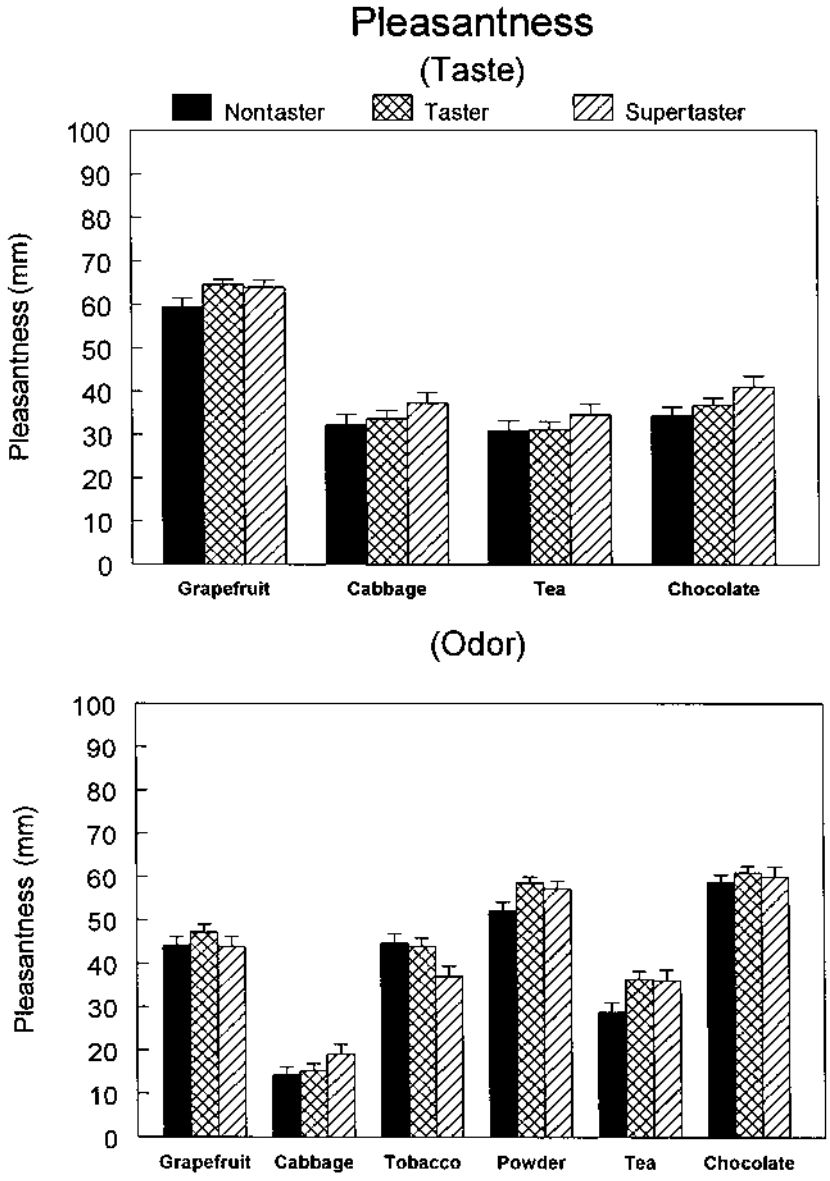

Figure 2 Taste and odor pleasantness ratings of nontasters, tasters, and supertasters for fresh grapefruit, raw cabbage (taste), boiled cabbage (odor), brewed tea, semisweet chocolate; tobacco (odor only), and baby powder (odor only). No significant taster group differences were observed for any food or nonfood stimulus. Ratings were made on a visual analog scale.

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tained on the preferred concentration of a flavor component in a food, liking of foods with particular flavor principles, and preferred frequency of ingestion are only three facets, and each contributes unique information (8). Although it is widely accepted that the sensory properties of foods are important determinants of food choice, their effect is not limited to influences on initial palatability. Contributions to postingestive processing of foods and nutrients may also be important (67,50). Indeed, the latter role is much underappreciated given the fact that food choice is based more on recalled experiences with a food than its tested sensory properties. Humans generally do not sample foods before deciding which to ingest. In this regard, the 2002 report of bitter taste receptors from the T2R family in the gastrointestinal tract of mice and rats (68) is intriguing. Studies exploring metabolic processes in individuals classified according to PROP status may be fruitful for understanding hedonic responses to foods. Nonsensory factors such as health beliefs, convenience, and cultural norms also contribute to responses and may be prepotent. Nevertheless, at the present time, the literature provides very limited support for an association between PROP taster status and food acceptability.

V. 6-*n*-PROPYLTHIOURACIL TASTER STATUS AND FOOD INTAKE

The primary interest in elucidating the associations between sensory responsiveness to PROP and food constituents is to understand and allow modifications of food choice. The underlying assumption is that sensory properties are causally related to intake. However, because of the contributions of a plethora of nonsensory factors (69,70), such a relationship has proved difficult to document. Although significant inverse associations have been reported between bitterness and intake (e.g., (71), with only one exception, there are no data demonstrating differences in intake for specific foods linked to PROP taster status. The one trial with positive findings found that turnips and watercress (from an array of 13 vegetables) were consumed more frequently by PTC nontasters than by tasters (41). Negative results have been published from studies collecting self-reports of intake of vegetables (39–41), beer (4), and fruit, milk, coffee, chocolate, walnuts, diet soda, and oysters (40).

Few studies have attempted to explore the relationship between PROP taster status and total diet. With the hypothesis that PROP tasters

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and supertasters would be more sensitive to negative attributes in foods and, as a result, select a more restricted diet, we asked participants in our trial to rate their level of finickiness with respect to food choice on a 100-mm line scale. Although this trait was significantly correlated with BMI ($r = 0.25$, $p < 0.001$), no significant differences were observed between groups. On a 100-mm line scale (0 = "Not at all"; 100 = extremely) ratings were as follows: 67.6 ± 2.8 (nontasters), 64.4 ± 2.5 (tasters), and 70.7 ± 2.9 (supertasters). In 2002, Keller and colleagues (66) examined the reported frequency of intake of foods grouped according to the Food Guide Pyramid among 67 4- to 5-year-olds. No significant differences were observed for grains, fruits, vegetables, meats, dairy, or sweet/fat foods among the tasters and nontasters. Discretionary fat use was higher among nontasters (although not with correction for multiple testing). Only one study assessing total daily nutrient intake among individuals classified by PROP taster status was identified, and it revealed no differences (70). The lack of attention to the total diet is surprising given that individual foods hold little dietary importance unless consumed in great excess.

VI. 6-*n*-PROPYLTHIOURACIL TASTER STATUS AND BODY MASS INDEX

The paucity of evidence that PROP nontasters, tasters, and supertasters differ in food intake does not preclude the existence of differences in body weight or composition. Linking food intake to body weight is notoriously problematic because of methodological problems in documenting free-living consumption. Differences in lifestyle and/or metabolism that may alter energy expenditure and balance may also result in differences across PROP taster groups. However, the consistent observation is that there are no statistically significant differences in BMI (38,42,54,56,59,65,69,71–73). We also found no differences in our trial (Table 1). However, a 2002 study (74) reported that after controlling for disinhibition, unrestrained nontaster and taster women had higher BMIs than unrestrained supertaster women. No BMI difference was observed in restrained females. This observation highlights the multifactoral nature of energy balance regulation and the need for more sophisticated approaches to isolate the sensory contribution.

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VII. SUMMARY

Taken together, existing data provide little support for a causal relationship between bitter sensitivity, as indexed by PROP taster status, and food preferences, food choice, or nutritional status. To hold, this hypothesis would require, as a minimum, differential sensitivity or responsiveness to flavor compounds resulting in consistent hedonic responses that translate into altered food choice and, as a consequence, nutritional status. Support at each level is lacking. Recent studies indicate there are multiple bitter taste receptors and that sensitivity to PROP, a synthetic compound not present in foods, is unrelated to perception of numerous bitter food constituents. Data on PROP sensitivity and rated bitterness of whole foods are mixed. It is not surprising, then, that data on hedonic responses are also equivocal. Survey data are largely not supported by responses from psychophysical studies, and the latter reveal no consistent pattern of responses to specific foods. Where differences are noted, it is not clear that judgments are based specifically on taste. Odor may contribute. In the end, it is nearly uniformly reported that the dietary intake and BMI of taster groups do not differ. These latter findings also challenge arguments that PROP sensitivity is a useful marker for ingestive behavior. The inability to document taster group differences at each of these levels may be attributable to methodological issues related to PROP classification, hedonic testing, and dietary assessment or a true absence of group differences on these measures. Given the multitude of non-sensory factors that influence hedonic ratings, food choice and energy balance, at best, only a subtle effect seems plausible. This raises the question of whether and how research should proceed in this area. At present, it appears as though PROP tasting is a mechanism in search of a dietary phenomenon. It may be more productive to direct work towards documenting differences of relevant hard endpoints (e.g., oxidative or nutrient status) in taster groups which will then provide guidance and relevance to studies of contributory sensory influences.

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